# EXHIBIT D

**UNITED STATES DISTRICT COURT**
**SOUTHERN DISTRICT OF WEST VIRGINIA**
**AT CHARLESTON**

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| **IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION**<br><br>**THIS DOCUMENT RELATES TO WAVE 1** | **Master File No. 2:12-MD-02327**<br><br>**JOSEPH R. GOODWIN**<br>**U.S. DISTRICT JUDGE** |

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# SUZANNE PARISIAN, M.D.
# EXPERT WITNESS REPORT

## I. QUALIFICATION AND METHODOLOGY

### A. QUALIFICATIONS

1. Since August 1995, I, Suzanne Parisian, M.D., have been President of MD Assist, Inc., a regulatory and medical consulting firm specializing in matters involving the United States Food and Drug Administration's ("FDA") regulation of medical products. I received my Medical Degree (M.D.) from the University of South Florida in 1978, and am Board Certified in Anatomic and Clinical Pathology. I have over twenty-four (24) years of experience in the research and development of medical devices, biopharmaceuticals, and pharmaceuticals. I began my career, as a general physician practitioner, in 1980, and subsequently went into emergency medicine, where I oversaw all medical emergencies at Caldwell Memorial Hospital.

2. From 1991 to 1995, I served as a Commissioned Officer in the United States Public Health Service and achieved the rank of Lt. Commander. I was assigned as a Medical Officer to the FDA's Center for Devices and Radiological Health ("CDRH"). Concurrently, from l991 to l995, I was also assigned part-time clinical responsibilities at the Armed Forces Institute of Pathology ("AFIP"), Office of the Medical Examiner for the Armed Forces. At CDRH, from 1991 through March 1993 I was initially a Medical Officer in the Office of Health Affairs ("OHA") a staff office within the FDA to support a non-clinical Director of CDRH. I was primarily engaged in post-market issues for medical devices and protection of the public, including the FDA's oversight of the marketing of medical devices. In OHA I was required by my Supervisor to become versed with the Federal Food Drug and Cosmetic Act and its implementing regulations at FDA.

3. While in OHA, I was a medical officer charged to be responsible for identification and review of public health safety issues, which included voluntary and mandatory medical device reports ("MDRs") review of patient medical records, medical literature, marketing materials, scientific literature and labeling. I was also required to provide FDA's official comments on numerous United Sates and International medical device industry standards as well as guidance documents. Within OHA, I was the primary clinician assigned responsibility to preside over pro hoc meetings for 162 health risk assessments. The assessments were made to advise FDA and CDRH on overall health risk of medical devices' performance issues, help with identification and then communication of public health safety issues, and to make recommendations to FDA regarding subsequent regulatory and medical actions that should be undertaken by FDA, health care providers, users groups and manufacturers in order to help protect the public's welfare. (21 C.F.R. part 7). I was involved in several mandatory medical device recalls and participated with members of FDA's Office of General Consul in development of evidence and obtaining outside medical expert witnesses for a formal regulatory hearing. The mandatory recall actions required me

to review company manufacturing documents as well as company internal documents and employee testimonies. I also served as CDRH's medical expert testifying on behalf of the FDA.

4. In March 1993, the Commissioner of the FDA re-organized CDRH, transferring all medical officers to the Office of Device Evaluation ("ODE"), a pre-market review office for new products. I was one of a handful of medical officers at CDRH and ODE, officially assigned to ODE's Division of Reproductive Abdominal, Ear, Nose and Throat, and Radiology, ("DRAERD"). Within months, I was next made one of two Chief Medical Officers in ODE, now also involved with interacting with other government agencies, industry, the press, health care providers and the public, training ODE clinical personnel and staff regarding the FDA process and requirements, and for a time continuing my role from OHA for health risk assessment process for marketed devices. While in ODE, I performed an additional 100 health risk assessments and trained medical officers as to the procedure for conducting a health risk assessment.

5. ODE, FDA is the Office within CDRH responsible for the premarketing evaluation of product applications submitted by the manufacturer (sponsor) requesting to market new devices within the United States. At ODE, I participated in the review of clinical trial applications and marketing applications including Investigational Device Exemptions (IDE), 510(k)s, Premarket Approval Applications (PMAs), (and for Center for Biologics IND (Investigational New Drug Applications)) and submissions for Combination Products as well as assigned responsibility for training new medical officers and scientific reviewers in application and labeling review at CDRH. I was made an instructor in CDRH's Staff College for instruction of CDRH's reviewers in the design and evaluation of clinical data contained within premarketing applications.

6. Regarding post-market surveillance of marketed products while at the FDA, I participated with FDA's District Offices, Office of General Consul, and the Office of Compliance in the review of manufacturing records, product complaints and adverse event reports obtained by FDA. I was the primary clinician involved in several of FDA's Major Corporate-Wide actions, for which I received various honors for my service at the FDA, including Employee of the Month for the Department of Health and Human Services. I received multiple Unit and Individual Medals from the United States Public Health Service, including two Commendation Medals. I was sent by FDA as its official representative to medical and industry meetings inside and outside the U.S. to help instruct professionals about the regulatory requirements of the FDA and to help FDA monitor the conduct of FDA-regulated manufacturers and distributors for deviations from regulations governing promotional activities. I was also required to provide guidance to health care providers and industry organization as to the FDA's interpretation of food and drug laws as it pertained to FDA-regulated products and the role of manufacturers.

7. One of my assigned responsibilities at the FDA, based on my clinical training and experience, was to review facts contained in product marketing applications, clinical trials, medical literature, reports of post-marketing experience, and available manufacturing documents gathered by the FDA or provided to the FDA by the manufacturer or other

regulatory agencies. I was then to use those facts to: 1) make a clinical and regulatory determination to a reasonable degree of medical and/or regulatory certainty per the requirements of the FDCA and; 2) recommend the next courses of action available to help protect public health. I was also required by the FDA to advise and train other FDA employees regarding the review of facts of a case or issue, the requirements of the Food, Drug and Cosmetic Act, and in making a determination to a reasonable degree of medical and/or regulatory certainty regarding the clinical impact of the agency's actions on the public. This was a process I was trained in and required to perform for the FDA.

8. After leaving FDA in 1995, I founded a consulting firm initially called Medical Device Assistance, Inc. but later changed to 'M.D. Assist, Inc'. I have been president and chief executive officer of that organization since its inception. In this position, I have continued to provide information, advice, and guidance to individuals, trade groups, and professional organizations outside of the FDA regarding preclinical testing, FDA's requirements, Adverse Event Reporting, risk management, promotion and labeling of medical products. FDA convened a panel in 1997 to discuss methods to improve medical device labels, and invited me to participate in its panel of medical device labeling experts convened to provide comments on changes proposed by FDA. I have lectured at industry and medical conferences, seminars, colleges, and for medical societies regarding FDA, premarket clearance and approval, design of clinical trials and post-marketing issues including risk assessment, failure investigation, promotions, claims and product labeling. I am the author of a book titled FDA Inside and Out published in May 2001, which has been used as a college textbook and library reference describing the workings, laws and history of the FDA.

9. During my tenure at the FDA and in my current position as a regulatory consultant, I have reviewed hundreds of marketing applications for safety and efficacy as well as proposed draft labeling and commercial marketing. My medical device experience includes all classes of medical devices: Class I, II and III. In this capacity, I worked with industry scientists and academic clinical investigators for evaluation, marketing and labeling review of new products. I have a broad range of experience that spans multiple medical areas, including women's health, wound healing, gynecology, urology and toxicology to name a few. Both while at the FDA and after leaving the FDA I have been interviewed on several occasions by the press regarding women's health issues and the activities of the FDA. After leaving the FDA, I have presented on women's health issues and the role of the FDA to members of Congress and their staff.

10. As part of my twenty years as a FDA Regulatory consultant, physician and former FDA Chief Medical Officer, I have directly assisted industry (manufacturers/Sponsors) with product design and development, identification of predicates, use of voluntary industry standards, FDA's, International Conference on Harmonized (ICH) Technical Guidances for providing adequate documentation to FDA in a pre-marketing submissions( 510(k), IDE, PMA and PMA supplement). I have been consulted to create entire FDA submissions (510(k), IDE and PMA) for Sponsors using my own analysis of available medical literature, pre-clinical and clinical data, outcomes, as well as when available post-market information and draft labels and commercial marketing materials. Based on my training and experience

at the FDA and as a physician, I have been consulted by Sponsors on different types of preclinical and/clinical testing available for a new medical device, having to review published scientific and medical literature about the product, help select materials including for implanted products interpreting industry standards and FDA's guidances. I have designed protocols for Investigational Device Exemptions (IDE) (*as well as Investigational New Drug Applications- IND), adequate informed consents, investigators' brochures, and suitable methods for data collection, statistical methods to generate scientifically valid endpoints, monitor the various phases of clinical trials to ensure patient safety. I have also been used to investigate and evaluate adverse events and create periodic reports and communications for FDA. I have been designated as a Sponsor's primary regulatory consultant with FDA on numerous occasions, and have also been used to facilitate meetings between a Sponsor with appropriate members of FDA's ODE staff, assisting a Sponsor to specifically discuss and negotiate contents of future marketing applications which may be acceptable to FDA. I have provided my expertise to train Sponsors' own regulatory, clinical and marketing staff in the relevant FDA regulatory processes needed for marketing its medical device in the United States including requirements for post-market surveillance, medical device reporting, failure investigation and recordkeeping. I have been utilized by Industry and Sponsors based on my training and experience as a former FDA medical officer as the company's proxy "face of the FDA" (sounding board) to help it better design presentations and interactions with the FDA for both pre-market and post-market issues. I have also been used by Sponsors to help its quality and regulatory staff look for and then troubleshoot potential safety issues occurring with its medical devices in terms of my review of adverse events, complaint files, manufacturing and the medical literature.

11. My most current curriculum vitae is provided in Attachment "1." I charge $400/hr. per study and $600/hr. for testimony and court.

## B. METHODOLOGY

12. I continue to use the same methodology for clinical and regulatory review I was first trained to use while at FDA as a medical officer with consideration of the Federal Food Drug and Cosmetic Act, implementing regulations, global industry standards, in addition to my training as a physician, to analyze the role of Ethicon as a United States medical device manufacturer of a permanently implanted medical device, clinical and scientific information available, quality system regulations applicable to Ethicon's design, testing, risk management, and implementation of manufacturing process controls for its pelvic organ prolapse ("POP") Prolift/Prolift+M products. Regarding the regulatory history of Ethicon's commercial (post-market) Prolift/Prolift+M products, I have considered Ethicon's handling of complaints, statistical trending, marketing and communication of risk to health care providers and patients, sales force feedback, post-market surveillance practices and patients' outcome and known and knowable risk information. I have continued to use that same methodology as a regulatory consultant for more than twenty years whether for industry or for litigation support.

13. My regulatory opinions are based on confidential Ethicon documents, employee testimonies, scientific and product design development and testing as well as public information

including FDA's documents, global industry standards and issues for similar products. To formulate my expert opinions for Prolift/Prolift+M and actions of Ethicon, based on my training and experience as to the requirements for a United States manufacturer like Ethicon, I have reviewed the medical literature, internal Ethicon documents, employee testimonies, design, testing and marketing documents for Prolift/Prolift+M as well as similar Ethicon pelvic products, various studies associated with synthetic surgical mesh including mesh implanted transvaginally in the female pelvis, Ethicon's goals for device performance characteristics and acceptable properties, quality systems and manufacturing documents including Ethicon's internal risk management, device Failure Modes and Effects Analysis (dFMEA) and its interactions and representations to its sales force and marketing to physicians and women. My regulatory opinions will be focused for each plaintiff on the relevant case-specific depositions and her timeframes as to Prolift +M implantation and when applicable, explanation, including timing, reports of the operative findings and additional surgery(ies).

14. My opinions are not intended to address medical causation or standard of care in terms of the treating physicians. I have employed reasonable methods and when relevant have also relied on global industry standards and applicable recommendations of the Global Harmonization Task Force ("GHTF"), French National Authority for Health ("HAS"), National Institute for Health Care Excellence ("NICE"), International Organization for Standardization ("ISO"), International Electrotechnical Commission ("IEC"), and the Asian Harmonization Working Party ("AHWP"), all of whom are liaison body members contributing to the GHTF. These organizations along with FDA have helped develop a series of inter-related documents and accepted actions for voluntary adoption and use by an international company like Johnson and Johnson's Ethicon to help harmonize medical device development. In terms of Ethicon's marketing of Prolift+M in the United States, I rely on my own experience as an American trained physician and FDA regulatory expert, the FDA's history of Prolift+M's clearance, which permitted commercial marketing. My expert opinions are formulated using the same methodology I first learned to use at the FDA for pre-market and post-market review and it provides the overall support for the expert regulatory opinions that I plan to offer regarding Prolift+M.

15. As part of my standard methodology, I have conducted my own review of FDA's database, including the FDA Advisory Committee Transcript for the September 2011 meeting on pelvic organ prolapse (POP) and SUI, and the U.S. medical literature through the National Library of Medicine's database to obtain documents pertaining to the use of the transvaginal mesh (TVM) for treatment of stress urinary incontinence (SUI) as well as for the POP and Ethicon's Prolift +M product. I have reviewed Ethicon and Prolift/Prolift+M and POP documents available to me within the public database in terms of support for regulatory opinions and my development of a regulatory timeframe for Ethicon's actions for its POP products that will be related to each plaintiff. The product materials that I have reviewed in this matter are the exact same types of materials that I have been preparing or reviewing to ensure their accuracy, truthfulness, and their entirety during my professional career. Therefore, I am familiar with the types of documents reviewed here and Ethicon's regulatory responsibilities to physicians, consumers, and general public in this case for its commercial Prolift+M product.

a. I have been asked to address the actions of Ethicon in the context of the company's responsibilities as the United States Manufacturer of the TVM Prolift+M System for POP. This product was eventually cleared by FDA to be legally marked in the United States as a pelvic floor repair (PFR) system procedure kit for management of symptoms of POP.

16. During the preparation of this Report, I additionally reviewed, consulted, and relied upon the following categories of information, listed in my reliance list, which include: internal Ethicon documents produced in this litigation; relevant scientific and medical literature; trial and/or deposition transcripts (and exhibits)(documents I located on-line, which include a review of Johnson & Johnson's website; and other relevant websites, including the FDA's 510(k) database and MAUDE database; and applicable statutes, regulations and guidance documents; premarket notification 510(k) documents including the predicates; other 510(k) Summaries relevant to the Prolift/Prolift+M products development histories.

17. My expert regulatory opinions utilize the same techniques, processes, methods and types of documentation used by other FDA regulatory experts. My opinions also rely heavily on my training as to FDA's and industry's use of voluntary industry standards to assist in development and support of products as well as procedures for manufacturing and marketing, discussed above. My opinions also rely on my medical and scientific training and post-market experience at FDA with health risk assessment and evaluation, voluntary and mandatory recalls, toxicology, biomaterials safety notification and my professional experience, permits me to incorporate the health risk (clinical impact) of Ethicon's regulatory actions with Prolift+M in the public. This impact on the public would also be seen in terms of Ethicon's adherence (or lack of adherence) to various industry standards and Ethicon's documents regarding FDA's minimum requirements and its own adherence to internal operating procedures for ensuring current good manufacturing practices of the quality systems regulations (GMP/QSR) in its manufacturing, post-market monitoring, failure investigation, complaint handling, corrective and preventive actions (CAPA) and voluntary actions to inform physicians and protect women. Just as I was first requested to do at the FDA and I continued to do for manufacturers after FDA, I review each document or testimony within a regulatory framework to make a determination if it is an example of acceptable or not acceptable behavior in terms of the Food Drug and Cosmetic Act and specific implementing regulations for a manufacturer. When also viewed in the medical and scientific context does a company's action provide evidence of a potential known or knowable risk in term of patient safety. This two-prong evaluation is no different from what I have been doing for the past twenty-four (24) years. In essence, I reviewed the background research and science, information available, formulated theories, tested my theories against the information that I reviewed here while heavily relying on the FDA's regulations and through my knowledge, experience, training at FDA, and regulatory expertise coherently communicated my conclusions in this Report.

18. Over the course of my career, I have been an integral member as a regulatory consultant for multiple companies and review teams, where together we determined whether the products would be sufficient to meet FDA's regulatory requirements and global industry standards.

As part of this analysis, I would consider whether additional studies/testing was required, and, if additional studies/testing was required, what types of studies/testing were necessary. Additionally, I determined whether the proposed device label, labeling, instructions for marketing was adequate and all-encompassing for the provider according to the various industry and regulatory standards and my training and experience. For example, in my post-market role as the Medical Officer in OHA, I was required to provide FDA's official comments and participate with various international and national industry groups to help develop industry standards' for FDA-regulated medical devices. Since leaving the FDA there were many years when I continued to be a regulatory and medical expert on industry standard committees involved with design, development and critique of various types of voluntary medical device industry standards. I have often been asked to evaluate the types of proposed testing/studies for a manufacturer as related to industry standards for manufacturing and clinical trials needed to obtain patient data and update labeling and marketing and training even when clinical studies were not required under FDA's guidelines to obtain 510(k) clearance. I have utilized clinical trials and studies (clinical data) to inform companies and physicians about the risk/benefit ratio of a particular product or types of products, which assisted them in the creation and updating of IFUs, training materials, methods for risk management and updating of marketing materials, which had to be consistent with both the potential risks and benefits of a new or marketed device or product and FDA's pre-market clearance (approval) and intended use. I have presented on US medical devices to foreign regulatory agencies as well as foreign medical organizations as to how products were evaluated in the United States, the use of the product in patients, labeling requirements for the FDA, as well as helping that regulated industry obtain acceptance and reimbursement by foreign regulatory agencies. I also had to have a working familiarity with United States and International standards and requirements to help a Sponsor harmonize its products for effective marketing both in and outside the United States.

19. My analysis of the Prolift +M factors in a multitude of sources of information always in the context of the FDA requirements and public health for marketing in the United States and are no different than those I have employed throughout my career for medical product research and development and marketing.

20. In addition, beginning at FDA I became directly involved in the writing and review of Dear Health Care Provider Letters, FDA Safety Alerts, Public Health Notifications as well as Briefing materials and presentations made to FDA Advisory Committee Panels to discuss safety issues and express FDA's concerns for products. I have worked on labeling and marketing materials for companies, informed consent, training materials, investigator brochures and patient marketing. I was first instructed on the methods of regulatory evaluation to ascertain the adequacy of labeling and warnings for CDRH's Office of Compliance. The review would include the adequacy of labels (including IFU and physician training manual) in terms of the regulations including, advertising and marketing when intended for health care professionals,(including adequacy of prescription labels), as well as for patients, Direct-to-Consumer marketing to the public and labeling and Instructions for Use (IFU) for the home health care environment while at OHA. I was also required to review for FDA the medical and scientific literature, patient case reports and adverse events, and medical device reports (MDRs), and to identify off-label and/or

unsupported claims and marketing by industry and provide recommendations to FDA for actions by the Agency and changes to labels, marketing and warnings. I continue to do all these same functions today both for industry and litigation support.

21. I have presented at industry meetings about the FDA and its processes and requirements. I have trained college students, including engineers, going into the medical device industry. I have trained medical students, residents and physicians about the regulatory process, clinical trials, adverse event reporting and risk assessment. I am the identified resource for the Arizona Medical Association to interact with the media for issues dealing with FDA. For the Regulatory Affairs Professionals (RAPS), I was an instructor in its online course on FDA and Medical Devices. Moreover, I have worked with companies and their adverse event evaluation staff to identify safety signals in complaint files and manufacturing records and discussed how to best deal with post-market safety issues and interaction with the FDA, physicians and the public.

22. Specifically for Johnson & Johnson, I was invited to present at one of its National Sales Meetings about the FDA process and instruct its employees on how to investigate and report safety issues (adverse event reports) for drugs and devices.

23. Finally, for clarification, I intend to offer no unsupported subjective opinions regarding Ethicon's intent or state of mind. I also intend to offer no case specific medical causation or medical standard of care opinions regarding a particular plaintiff.

## II. OVERVIEW OF REGULATORY PROCESS AS BASES FOR OPINIONS

24. The FDA was given responsibility to be the gatekeeper for the public for new medical devices entering the United States market by Congress through its passage of the Medical Device Amendments (MDA) of 1976 to the Federal Food Drug and Cosmetic Act. As the assigned gatekeeper, the FDA was required to establish methods to regulate medical devices similar to human pharmaceutical drugs with both pre-market review phase and post-market requirements for the sponsor with the commercial product. The FDA was required to establish a method for pre-market review to show acceptance that a product met a certain regulatory standard to start marketing in the United States. The FDA's role was also to establish minimal standards for Good Manufacturing Practices (GMP) as well as the marketing claims that could be made for a new product in the United States based on scientific information. GMP requirements of 21 C.F.R.§ 820 was later amended by the Safe Medical Device Amendment (SMDA) of 1990 to include new emphasis on industry's use of pre-market design controls and risk management, now called Quality System Regulations (21 C.F.R. § 820).

25. Most new medical devices, not specifically exempted from FDA's pre-market review, usually enter the market by either obtaining a 510(k) clearance or through Premarket Application Approval (PMA). Ethicon was able to legally market the Gynecare Prolift and Prolift+M Total, Anterior, and Posterior Pelvic Floor Repair System based on its successful submission of Ethicon's 510(k) application (K071512) on June 4, 2007 that was cleared by the FDA on May 15, 2008. The new device itself was not required to be submitted to FDA,

nor did FDA conduct any physical laboratory or patient testing. Ethicon as the expert in its new proposed device claimed in its 510(k) submission that it had determined its new Prolift+M was substantially equivalent to other already cleared and marketed devices.

26. I will further describe the Prolift+M 510(k) clearance process and the history of Ethicon's interactions with FDA and physicians. Based on the information reviewed, Ethicon did not take the reasonable care of a United States medical device manufacturer to ensure its own compliance with the Federal Food Drug and Cosmetic Act, design a safe and effective permanently implanted Prolift or Prolift+M product for POP. Ethicon did not provide adequate risk information to FDA, physicians or to women. Ethicon did not determine and adequately describe safety and efficacy issues it knew were occurring for its Prolift or Prolift+M to FDA and even more importantly it failed to describe the risks to physicians and women. Ethicon also engaged in violative promotion activities with the Prolift Kit for POP. Ethicon's actions with both Prolift and Prolift+M misbranded the product when it failed to monitor commercial performance to update physicians with risk information. Also Ethicon's marketing and implied to physicians that its 510(k) cleared Prolift+M had been found to be 'safe and effective.' This representation by Ethicon grossly overstated the oversight role of the FDA in Ethicon's clearance to market Prolift+M.

### A. THE § 510(K) CLEARANCE PROCESS VERSUS PREMARKET APPLICATION APPROVAL (PMA)

27. Medical devices were subjected to regulation after commercial use (post-market) under the Federal Food, Drug, and Cosmetic Act (FDCA or 'Act') of 1938. However, until l976, there were no requirements that devices be reviewed or approved by FDA "before they were actually commercially distributed" (i.e. pre-market) in the U.S. Prior to 1976, device regulation was defined only by the FDCA's misbranding and adulteration provisions, similar to the way foods and cosmetics are still regulated, and the agency's regulation of medical devices was 'after the fact' or after a safety issue occurred. FDA had been given no legal authority to keep unsafe medical devices from entering U.S. commerce prior to 1976. In some rare instances, FDA was able to provide oversight for selected new medical devices through premarket review authority by using the drug regulations as 'new drugs'. For example, Johnson & Johnson's PROLENE suture was originally regulated as a new drug through drug regulations requiring FDA pre-market approval of a New Drug Application. (NDA) The situation for medical devices changed when Congress enacted the Medical Device Amendments (MDA) of l976 to the Food, Drug and Cosmetic Act (FDCA), which finally gave FDA the authority to require a pre-market review for medical devices before entering the market. Medical devices like Johnson & Johnson's Prolene suture were then transitioned to regulation as medical devices, and called Pre-Amendment transitional devices. The approved NDA for Prolene suture was changed (transitioned) to an approved Premarket Approval Application (PMA).[1]

28. The FDA implemented a risk based system for classification of medical devices starting in 1976. This system classifies medical devices into one of three regulatory classes based on

[1] Ethicon's Prolene suture with the approved PMA was later reclassified (down-classified) by FDA to class II so that it could be marketed by clearance of a 510(k).

the level of risk associated with the device for the public and the amount of manufacturing control necessary to ensure that the device is safe and effective for its intended use.[2] Devices which appear to pose the lowest risk for the public and require the least amount of manufacturing control, are placed as a Class I device and receive the least regulatory oversight and are applicable to general manufacturing controls. Class II devices pose greater risks for the public, require increased controls in terms of manufacturing, as well as monitoring and labeling. Class III devices are considered the highest risk or require the greatest amount of FDA oversight before marketing. Ethicon's Prolift/ Prolift+M were cleared together by the same May 2008 510(k) as Class II devices. FDA is now proposing to reclassify the TVM POP devices into Class III to require PMA approval before marketing based on risks to the public.

> **Class I**- General controls: Regulates devices for which controls other than special controls or premarket approval are sufficient to assure safety and effectiveness. Such controls include regulations that (1) prohibit adulterated or misbranded devices; (2) require domestic device manufacturers, initial distributors, and distributors to register their establishments and list their devices; (3) grant FDA authority to ban certain devices; (4) provide for notification of risks and repair, replacement, or refund; (5) restrict the sale, distribution, or use of certain devices; and (6) cover Good Manufacturing Practices (GMP) or Quality Systems Regulations (QSR), records, reports, and inspections. These minimum requirements apply to all classes of FDA-regulated devices.
>
> **Class II**- Special controls: Regulates devices for which general controls alone are not sufficient to provide reasonable assurance of safety and effectiveness and for which sufficient information exists to be able to establish special controls that are necessary to provide this assurance.
>
> **Class III**- Premarket Approval: Regulates devices for which insufficient information exists to determine the general controls and special controls that will provide reasonable assurance of safety and effectiveness. Generally, class III devices are those represented to be life supporting or sustaining, those implanted in the body, or those presenting potential unreasonable risk of illness or injury, or those devices were there is insufficient information for FDA to determine the potential safety and effectiveness.

29. Class I and II devices are often brought to the United States market through a premarket notification process, called a 510(k) application. Over time and to help reduce agency expenditure of resources, FDA has exempted most Class I and many Class II devices from a requirement for obtaining 510(k) clearance by FDA before start of marketing, with general and specific controls still applicable for the sponsor of the product. The riskiest devices, devices with the least scientific information known about performance and/or manufacturing controls necessary to ensure they are safe and effective, or 'pre-Amendments' devices on the

[2] 21 C.F.R. § 860.3.

market before 1976 earmarked for later review by FDA, are devices requiring the greatest FDA resources and oversight by FDA and industry and are classified as 'Class III'.

30. Generally, Class III devices cannot be brought to market until a sponsor legally completes a successful Premarket Approval ("PMA") process. These Class III devices are to be approved by FDA as supporting safety and efficacy based on scientific evidence for specific indications. The PMA approval process, unlike the standard 510(k) clearance, includes FDA's approval of a sponsor's proposed manufacturing controls, a clinical investigation with clinical data able to support the proposed success criteria, the sponsor providing its draft labeling and post-marketing requirements (21 C.F.R. § 814). PMA approval usually requires submission of a series of clinical trials with patient data obtained in the United States under an FDA approved Investigational Device Exemption protocol (IDEs) (21 C.F.R. § 812). The IDE also has a requirement for the participant in the trial to give adequate written informed consent to participate (21 C.F.R. § 50) and Institutional Review Board (IRB) oversight, monitoring and reporting (21 C.F.R. § 56). The IDE process was established by Congress and FDA to ensure that medical device research is conducted ethically and that patients are informed of the risk and willing agree to participate.

31. In contrast to the PMA which is required for a sponsor to obtain FDA's approval of a new device or technology or claim, the 510(k) sponsor must provide an application that can indirectly support safety and efficacy for an intended use. A 510(k) application is a premarket submission (paper application) made to the FDA in which a sponsor (the expert for the product) attempts to support that its new proposed device it intends to manufacture when it is commercially marketed for an intended use is substantially equivalent (SE) to an already legally marketed device (commonly referred to as a "predicate" device) sold for the same intended use.[3] The sponsor of the new proposed product, based on successful support of substantial equivalence for same intended use to the FDA, within the 510(k) process can rely (bridge) on the history of safety and efficacy of it already cleared commercial marketed device (predicate). The 510(k) process results in an FDA marketing 'clearance' not an FDA 'approval' for a sponsor to start marketing a new product. The FDA's 510(k) review is required, by regulation, to be completed by the assigned FDA Office of Device Evaluation (ODE) reviewer within 90 working days.[4] The FDA's ODE (Pre-market) review will focuses on the sponsor's information in the 510(k) as to whether the new device shares the same intended use, design, materials, or other characteristics of the predicate device. The FDA reviewer, who is usually a scientist but not clinically trained, is to be adequately informed by the submitting sponsor, viewed as the expert in the product, if there are new issues of safety and effectiveness which still need to be addressed by the sponsor for the new device when compared to the marketed predicates. As industry is aware, the 510(k) process relies on an FDA Reviewer's completion of a 510(k) Substantial Equivalence Decision-Making Tree Flowsheet which is kept as part of the official FDA record. Based on the information inserted into the decision tree by the reviewer, the sponsor may be requested to

[3] *See* Premarket Notification, U.S. Food and Drug Administration, available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm] (last visited July 14, 2015).
[4] *Id.*

provide additional information (AI) or address new issues of safety and effectiveness now present with the predicates cited.

32. The FDA reviewer within certain limits can request additional information (AI) for the 510(k) from the sponsor to address substantial equivalence of the new and predicate devices, and may place the application on hold. However, the number of times that information is requested is limited for FDA's reviewers and the testing requested must be able to be justifiable in terms of testing required of other sponsors for similar products. (i.e. level playing field). Therefore, there are limitations as to what the FDA reviewer is permitted to request from a sponsor like Ethicon for the Prolift/Prolift+M 510(k). Also, there is an emphasis at CDRH ODE in completing 510(k)s and making a decision about ability to clear within 90 working days. Each round that a reviewer holds a 510(k) for AI is tallied and reviewed by FDA's upper management and will directly impact the ODE employee work review history. Time until completion of 510(k)s is also presented to Congress each year and will directly impact the annual payment of Medical Device User Fees by industry. MDUFA fees are paid to FDA for CDRH use based on support of agency efficiency.

33. Clinical trials are generally not required to substantiate the safety or effectiveness of a device submitted pursuant to the 510(k) process. [5] However, there are times when preclinical testing, including laboratory and animal studies, and/or clinical data (human data) are required from the sponsor to be able to address for the FDA potential new issues of safety and effectiveness for its device design, performance or intended use. For a 510(k), as with a PMA, for a sponsor to obtain clinical data legally with United States patient requires the clinical study to be conducted under an IDE, with the patient receiving and signing an adequate informed consent and Institutional Review Board oversight, monitoring and reporting (21 C.F.R. § 50; 21 C.F.R. § 56).

**1. Investigational Device Exemption (IDE): 21 C.F.R. § 812**

34. A Sponsor who knows a new device is not "substantially equivalent" to a pre-Amendment device or who is not sure if a device is "substantially equivalent" without conducting a clinical investigation must obtain an FDA approved IDE to ethically conduct the clinical investigation in the United States. After collecting clinical data, a sponsor who desires to market a device must either submit a premarket notification (510(k)) or premarket approval application[6] to FDA. A premarket notification may be submitted if the sponsor believes the data supports a finding of substantial equivalence.

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[5] *Id.*

[66] Product Development Protocol or 'PDP' is another less-frequently used pre-market route for obtaining FDA's approval for marketing. The PDP entails a series of pre-agreed (*between the sponsor and FDA) upon development and testing protocol and description of the outcomes capable of supporting the ability of FDA to approve a new product for marketing. The PDP is called "completed" when all evidence of success for pre-agreed upon parameters have been met. The PDP is also referred to as approved when the FDA determines the PDP has been completed and the outcome is successful. Both the PMA and PDP are described by 21 CFR § 814. The PDP is used as a less frequent pre-marketing route due to the increased involvement of the FDA in the process and its requiring fulfillment of specific pre-agreed success criteria.

35. The Investigational Device Exemption (IDE) was reportedly designed by Congress to ensure that valid scientific information (21 C.F.R. § 860.7) can be "legally and ethically" obtained by a sponsor while ensuring public safety. An IDE ( 21 C.F.R. Part 812) requires that a product's sponsor first obtain FDA's approval of an investigation device exemption (IDE) for a significant risk investigation request prior to beginning distribution of an investigational product for a human trial in the United States. The purpose of clinical investigations done for FDA with an IDE is that a sponsor may eventually submit a marketing application to FDA for support of premarketing clearance or approval of a new device and/or of a marketed device's new indications. A clinical investigation involving the implantation of a permanently implanted device, such surgical mesh for pelvic organ prolapse, is a significant risk study. In a human population in the United States it would constitute a significant risk investigation and is required to be legally done by the sponsor first obtaining FDA's approval of an IDE.

36. The Investigational Device Exemption (IDE) technically "exempts" an investigational device from certain requirements of the FDCA in order to allow for legal interstate transport and distribution of a product that is not yet in full compliance with the FDCA. The IDE exempts the 'investigational' device from fulfilling the FDCA's requirements for misbranding, premarket notification, and certain good manufacturing practices. To help further the development of new medical devices for the public, once an IDE application is submitted to the FDA, the agency has a mandatory 30 days to either approve or deny a requested IDE protocol or the protocol will be automatically approved. There are no fees for industry required for FDA's review of IDEs.

37. IDEs can be 'conditionally approved' with an FDA letter requesting additional information or changes to the proposed protocol or handling of the data. The conditionally approved IDE is able to be started by the sponsor, but the conditions must be met for the IDE. IDEs can also be denied by the FDA, however, the FDA's letter to the sponsor must clearly provide the sponsor with guidance as to why the IDE request was denied and changes necessary to permit the IDE to be approved.

38. Without first obtaining approval of an IDE, a sponsor who begins or encourages clinical investigations in United States patients for significant risk investigations, without obtaining pre-marketing approval or clearance, is in violation of the FDA's laws, a Prohibited Act by the FDCA. By FDCA, a U.S. manufacturer (*a sponsor) is held responsible to FDA for maintaining control and accountability of its investigational device (i.e. unapproved or not cleared indication, Class III) and for monitoring the conduct of its investigations and safety of the public.

39. Controls to protect the safety and rights of patients include the sponsor obtaining FDA's approval of a proposed IDE protocol (plan) to ensure the quality of the information developed and safety of the subject and that adequate data will be generated for either clearance or approval. The IDE protocol has pre-established success and failure criteria and a written plan for a specified number of subjects (inclusion and exclusion criteria) and when the protocol will be stopped. Another requirement for an IDE is that the patient as a participant in an IDE study, has treatment converted from a physician's 'patient' to an

investigator's 'subject'. Each subject enrolled in a clinical trial under an IDE must be given an opportunity to provide and sign adequate informed consent agreeing to voluntarily participate in the proposed study. The informed consent must include a statement that the proposed product is 'investigational' and safety and effectiveness has not yet been determined. In a Sponsor's clinical investigation, the physician becomes a 'clinical investigator' for the Sponsor, no longer simply treating a patient. In return, the Sponsor is required to provide adequate risk information to the investigator. The clinical investigators must sign an agreement to participate in a clinical study for the Sponsor, and will adhere to the approved protocol. Finally, as an extension of the FDA's process for ensuring patient safety, there is required recordkeeping, periodic reporting, oversight and monitoring of the clinical investigation progress by an Institutional Review Board (IRB). An approved IDE protocol will require periodic reporting to both FDA and the IRB by the investigators and Sponsor and there will be required follow-up documentation for the outcome of each subject enrolled. Ethicon as a major medical device manufacturer is aware of and has fulfilled IDE requirements for conducting some of its research in the United States. Physicians and patient must be advised by a Sponsor when they are both participating in a Sponsor's product development.[7] The Sponsor is the entity which will profit from the research conducted in humans with its device.

40. When clinical data is obtained for a significant risk device in United States patients, particularly permanently implanted devices and provided to the FDA in pre-marketing applications such as 510(k)s, it was required to have been obtained ethically under an approved IDE. However, as Ethicon would be aware, members of FDA's ODE pre-market staff, particularly members with surgical devices, are to complete application review within the 90- days timeframe. This group of reviewers have been openly criticized for not following-up on how certain clinical data was obtained by a sponsor using United States patients without evidence of an approved IDE. It could be a role of ODE reviewers, a role usually not pursued, to identify if a Sponsor had encouraged or promoted physicians or had any involvement using their own patient populations 'off label' to obtain clinical data for the Sponsor outside an FDA approved IDE. FDA will always accept human safety information, but efficacy information with United States patients is to have been obtained using the IDE process. FDA has noted shortcomings, often based on limited resources, in its premarket review, postmarket surveillance and oversight of medical device manufacturers.[8]

41. When Ethicon submitted the original PROLIFT+M 510(k), FDA's ODE reviewers became aware that Prolift had been marketed "off label" for years by Ethicon for POP without 510(k) clearance or an FDA approved IDE. Yet, the pre-market ODE Branch pursued no official regulatory action or civil penalties against Ethicon for its violation of the Act. ODE permitted Ethicon to add Prolift to its Prolift+M 510(k) submission. This was done at the regulatory discretion of the ODE Review Branch, and in the past is a decision based on FDA's resources and the costs to the public. Normally, a post-market action for off label

[8] GAO testimony before the Subcommittee on Health Committee on Energy and Commerce, House of Representatives Medical Devices: Shortcomings in FDA's Premarket Review, Postmarket Surveillance, and Inspections of Device Manufacturing Establishments. Statement of Marcia Crosse, Director, Health Care June 18, 2009.

marketing falls to FDA's Office of Compliance (OC), not members of ODE. There is no description of ODE involving OC as it attempted to complete the 510(k). However, the FDA's ODE did inform Ethicon that a 510(k) was needed to begin to market Prolift for POP and that 510(k) clearance was required before Ethicon could continue to market Prolift. Therefore, despite the FDA's lack of an apparent official regulatory taken action against Ethicon, there is documentation in the FDA's record that Ethicon had not complied with the Act when it began marketing Prolift without a 510(k). The FDA documents also show that ODE staff did not elect to follow-up on how data had been ethically and legally obtained from United States patients without the safeguards of an FDA approved IDE for a significant risk device. Again there is clear documentation of lack of Ethicon compliance with the IDE regulations for investigation of Prolift and ethical research in American women, but with FDA's ODE opting to not pursue a course of regulatory actions against Ethicon.

42. Any action by a Sponsor which encouraged, promoted off-label – investigational- (not cleared/not approved-Class III) use of a new product or an already cleared product for a new indication is not in compliance with the Act and, whether there is official regulatory action taken by FDA or not, it is still an example of misbranding and marketing of an adulterated device without an IDE and a violation of the premarket clearance/approval process.

**2. Safe Medical Device Amendment of 1990 (SMDA)**

43. After a review of FDA's classification actions by Congress, which occurred during the mid-1980s and its detection of FDA's overwhelming reliance on the 510(k) pre-market notification process rather than the requirement for the more scientifically rigorous premarket approval applications (PMA)s and/or FDA's issuance of Performance Standards, Congress opted to accept FDA actions as valid and passed the Safe Medical Devices Act of 1990 (SMDA). At that time, Congress accepted the FDA's assurances that FDA's reliance on premarket notification (510(k)) process as the primary safety and effectiveness screen for new medical devices was valid. Congress however shifted the FDCA's focus away from premarket review by FDA to an increased emphasis on active postmarket oversight strategy for industry (i.e. mandatory adverse event reporting) for protecting the public's health.

44. The SMDA followed an eight year U.S. Congressional inquiry of the Medical Device Amendments of 1976 and the FDA's reliance on 'substantial equivalence'. The General Accounting Office (GAO) presented exhibits for the legislative review which defined the vulnerabilities of the 510(k) notification process. In that GAO review, it was identified that some qualified medical devices were disallowed testing in some instances, inadequately tested in a clinical setting and others deficient in adverse data collection and oversight by industry and FDA. The US Congressional review concluded that medical devices would require actual device experience in a clinical setting and sufficient reporting of adverse event data. There was a greater emphasis by SMDA placed on the post-marketing monitoring and submission of MDRs as well as improved design and risk management by industry instead of the prior emphasis on FDA premarket review.

45. Also, after SMDA, a predicate device could now be a device that could demonstrate that it had been legally marketed in the U.S. prior to 1976 for the same 'intended use' and for which FDA had not identified a safety and effectiveness issue. With rare exceptions, all pre-1976 devices (i.e. pre-Amendments) on the US market before 1976 were automatically grandfathered as safe and effective for the same intended use for which it was sold prior to MDA. All subsequent premarket notification applications or 510(k)s must include a distinct Summary of Safety & Effectiveness (SSE) section written by the sponsor (and not the FDA), that described the rationale for substantial equivalence or marketing clearance. That information is then published on the FDA's 510(k) website of cleared devices.

**3. Substantial Equivalence for the Same Intended Use to Support 510(k) Clearance**

46. At time of 510(k) review, if the FDA determined that a device was substantially equivalent (SE) to a predicate device(s) for the same intended use, the manufacturer will be given "clearance" to begin to market a product in the United States. Sales in the United States can begin when the sponsor receives a 510(k) clearance letter.[9] If the FDA cannot conclude based on the information received in the application that the device is substantially equivalent (SE) to any predicate or has a new intended use or raises new issues of safety and effectiveness that have not been addressed, the Sponsor receives a not substantially equivalent letter (NSE), with the new device classified as 'Class III'. As an NSE device the Sponsor, to eventually market a Class III device (or cleared device for a new Class III indication), is to proceed through the PMA route (or Product Development Protocol "PDP"). The Class III device (or indication) is to be first approved by FDA for marketing or to identify a different suitable predicate and resubmit a new 510(k). (21 C.F.R.§ 814).[10]

**4. Medical Device User Fees Based on FDA's Reviewer Time and CDRH's Resources**

47. The PMA process is unquestionably considered to be a more rigorous undertaking than the 510(k) process and as such it requires greater allotment of FDA's resources to complete. The Medical Device User Fee Act (MDUFA) calculates user fees annually for industry to pay based on FDA's reviewer time and Agency resources. The FDA's fee for a Sponsor in 2016 to submit an 'original PMA' for review and approval by FDA is: $261,388; a PMA 180-day supplement has a fee of $39,208; a real-time Supplement has a fee of $18,297; annual report review by FDA has the fee of $9,149; and a 30-day notice for FDA is $4,182. The MUFDA fee for submission and review of a 510(k) is: $5,228 (small business $2,614). There is no MDUFA fee for a sponsor's submission and review of an IDE application which is mandated to be completed by FDA within 30-days or automatically approved. A request for information from the FDA regarding the appropriate regulatory pathway is a called a '513(g)' which has the fee for industry to pay to the FDA of $3,529 (small business $1,765).

48. The PMA process at CDRH is analogous to Center for Drug Evaluation and Research (CDER's) New Drug Application ("NDA") process used for approval to market human pharmaceutical drugs or Center for Biologics Evaluation and Research (CBER's) Biologics

[9] *Id.*
[10] *Id.*

License Application ("BLA") process used to license the marketing of New Biologics.[11] Unlike the 510(k) clearance process, the original PMA, NDA, and BLA processes all require a lengthy application process, a series of clinical trials and must demonstrate the product's safety and effectiveness through supplying of valid scientific evidence.[12] Most often, these approval paths require manufacturers to conduct prospective controlled phased clinical trials. These approval applications must be reviewed by FDA's teams of reviewers, and if the Sponsor is successful, will result in FDA's approval (licensing) of a device, drug, or biologic.[13] All subsequent changes to an approved PMA, NDA, or BLA product are then made as PMA, NDA or BLA supplements to the initial application, again with user fees commensurate with the anticipated FDA reviewers' time and agency resources.

49. Manufacturers of marketed devices are also required to get the appropriate clearance or approval to introduce either a device into commercial distribution for the first time or to introduce or reintroduce a device that will be significantly changed or modified to the extent that its safety and effectiveness could be affected. New claims for an already 510(k) "cleared" device, or new indications for an already 510(k) cleared device occurring within labeling and advertising that may potentially alter safety and effectiveness are required also be reviewed and cleared (or approved) by FDA in a premarketing application prior to the start of legal marketing within the U.S. However, the Sponsor of a 510(k) cleared device can immediately update and improve its own label without any requirement for interaction with or approval from the FDA.

**5. Premarket Approval (PMA) Letter and Restrictions**

50. The FDA's PMA letter will include the restrictions for commercial marketing of the PMA-approved device. The sponsor's failure to adhere to the pre-market and post-market requirements for selling a product under an approved PMA may result in FDA's withdrawal of the PMA approval. The PMA approval also requires FDA to publish a summary of safety and effectiveness information (usually drafted by the Sponsor) it considered and on which the FDA's approval is based.

**6. PMA Supplements for Changes**

51. For an original PMA approval, the PMA supplement pursuant to 21 C.F.R.§ 814.39 will be used to make significant changes to the original PMA product, label or manufacturing. One approved original PMA (or NDA) can have years of subsequent changes made by FDA's approval of supplements. The PMA supplements will essentially show the evolution of the original product(s) over time. The same serial supplement process does not apply to the 510(k). Significant changes to a 510(k) product or changes to address issues with safety and effectiveness of the device require FDA's clearance of a new 510(k).

52. The FDA approves the Sponsors proposed draft label to ensure it reflects the accuracy of the information provided by the Sponsor and considered by the FDA to support product

[11] 21 C.F.R. § 814 *et seq*. (devices); 21 C.F.R. § 600-680 (biologics); 21 C.F.R. § 314 *et seq*. (drugs).
[12] 21 U.S.C.A. § 814.20; 21 C.F.R. § 314.50; 21 C.F.R. § 601.2.
[13] 21 U.S.C.A. § 360e; 21 C.F.R. § 814.40-814.47.

approval. The Sponsor of the PMA approved product (as well as the NDA approved product) retains the ability at all times to comply with the Act and protect the public. The Sponsor can immediately update its own label to improve and strengthen the warnings and instructions for use or to delete false and misleading information from the FDA's approved label. This ability to update and circulate the new label before obtaining FDA's approval of the changes is done using a Supplement process called a "Changes Being Effected" Supplement. (Drug- 21 C.F.R. § 314.70; Device- 21 C.F.R. § 814.39)

53. There is no restriction, other than accuracy and truthfulness, for a Sponsor to directly communicate risk information, warnings, changes in the instructions for use directly to health care providers by communications such as Dear Health Care Provider letters, training, KOL, and through its own sales force. The goal is for the Sponsor should be to ensure product compliance and that its product remains safe, effective throughout the anticipated lifetime of the product, adequately labeled and that the public remains protected.

**7. When 510(k) Changes Require A New 510(k) Clearance**

54. The 510(k) letter also describes the restrictions for sale of the cleared device, including the Indications for Use, as well as other actions required by the sponsor including establishment of QSR and adequate labels. The 510(k) process has no formal mechanism for FDA withdrawal or removal once a product is 510(k) cleared. The manufacturer essentially takes over all actions for oversight and marketing of its 510(k) cleared product. The PMA has approved product labeling which under certain circumstances should be updated by the sponsor. The 510(k) has been cleared by FDA for an indication for use and specific marketing claims. As stated in the 510(k) clearance letter, it is the sponsor that is directly responsible for ensuring its label remains adequate. The 510(k) sponsor for the majority of reasons, can immediately update and improve its label and marketing without receiving additional FDA input.

55. Significant changes to a 510(k), including ownership, changes which alter the intended use, new efficacy claims, change in the patient population, changes which raise new issues of safety and effectiveness and/or changes to a device made to address safety issues with a device are examples of when a Sponsor of a 510(k) cleared device is required to submit and obtain clearance of a new 510(k). When a Sponsor is in doubt if a new 510(k) is required, the FDA will provide guidance as to whether or not a new 510(k) is necessary. FDA also has returned submitted 510(k)s once it determined that a 510(k) submission was not necessary from a Sponsor.

**8. Sponsors of PMA and 510(k)s Share Common Duties Under Quality Systems Regulations (21 C.F.R. § 820)**

56. Both the PMA approval sponsor and the 510(k) clearance sponsor have shared responsibilities pursuant to the Quality System Regulations (QSR) for process controls, employee training, management responsibility, record keeping, post-market surveillance, maintaining complaint files, statistical trending and submission of Medical Device Reports (MDRs) to report adverse events and malfunctions to the FDA (21 C.F.R. 803). Both

sponsors share a common duty to update physicians and provide adequate and truthful warnings and instructions for use and ultimately ensure it continues to sell as safe, effective and adequately labeled device to the public. GHTF, noted that the purpose of adverse event reporting is the "protection of the health and safety of patients, users , and others by disseminating information which may reduce the likelihood of, or prevent repetition of adverse events, or alleviate consequences of such repetition."[14]

**9. 510(k) Clearance is Not Equivalent to PMA Approval and to Indicate Otherwise is "Misbranding"**

57. FDA's 510(k) clearance letter plainly states that "clearance" of a device through a 510(k) is not the same as "*approval*" of a device by (PMA). FDA states for a 510(k) letter that: "[s]ubmission of a premarket notification . . . *does not in any way denote official approval of the device. Any representation that creates an impression of official* ***approval*** *of a device because of complying with the premarket notification regulations is misleading and constitutes misbranding.*" 21 C.F.R. § 807.97.

58. Accordingly, 510(k) "clearance" and PMA "approval" are two distinct and separate processes and outcomes. For a manufacturer to represent a 510(k) cleared product is approved by FDA as safe and effective is by regulation "misleading" and constitutes "misbranding" of the device.

**B. FDA'S 510(K) PROCESS ADMITTEDLY HAS WEAKNESSES INCLUDING FDA'S REQUIRED RELIANCE ON THE '*TRUTHFULNESS AND ACCURACY*' OF THE INFORMATION IN A SPONSOR'S PRE-MARKETING APPLICATION**

59. Indeed, the 510(k) "clearance" process, as compared to an "approval" process, has undergone a great deal of scrutiny over the prior years. As discussed above, when the Medical Device Amendment was passed in 1976, it had been the expectation of Congress that the majority of medical devices would undergo the more rigorous PMA approval process or adhere to FDA-issued performance standards for that device before entering the market. Besides strengthening the adverse event reporting (AER, or MDR) requirements, Congress also chose to address the pre-market role of industry to ensure adherence to adequate design controls including pre-production design validation and methods of risk management implemented later as the Quality System Regulations (QSR) (21 C.F.R. § 820).

60. A variety of different independent analyses have continued to sound criticism of the 510(k) process and a call for substantive changes.[15] The resulting crescendo culminated recently in a FDA-requested analysis of the 510(k) process by the Institute of Medicine (IOM), a branch

[14] Final Document: Adverse Event Reporting Guidance for the Medical Device Manufacturer or its Authorized Representative, June 29, 1999 (GHTF/FD:99-7), Introduction.

[15] GAO testimony before the Subcommittee on Health Committee on Energy and Commerce, House of Representatives Medical Devices: Shortcomings in FDA's Premarket Review, Postmarket Surveillance, and Inspections of Device Manufacturing Establishments. Statement of Marcia Crosse, Director, Health Care June 18, 2009.

of the widely-respected National Academy of Sciences routinely contracted by FDA to provide it with outside expert recommendations. The IOM concluded that, "*the 510(k) process is flawed based on its legislative foundation*" and "*lacks the legal basis to be a reliable premarket screen of the safety and effectiveness…and cannot be transformed into one*."[16] These recommendations are not unique, and have been echoed by the U.S. Government Accountability Office (GAO), physicians, and consumer groups.[17] The 510(k) process has also helped lock manufacturing and materials in the United States for medical devices into pre-1976 materials. Reliance on pre-1976 materials helps a Sponsor like Ethicon avoid having to do testing to support the safety and effectiveness of new biomaterials when proposed to be permanently implanted in patients. As an example, polypropylene (PE) synthetic surgical mesh is based on 'pre-Amendments' surgical mesh, a screen-like material, used to repair gapping abdominal wounds temporarily during Korea and the Viet Nam War which was 'grandfathered' as safe and effective for use as implanted surgical mesh.

61. For a period of time and prior to advancements in toxicology, immunology, laboratory methods and microbiology, physicians considered polypropylene mesh essentially "inert" and well tolerated by the body. Science and follow-up has shown that the assumption that polypropylene was an inert material when implanted in the body was not accurate.

### C. ETHICON HAS A 'NON-DELEGABLE' DUTY TO DEVELOP, DESIGN, TEST AND SELL A SAFE AND EFFECTIVE AND ADEQUATELY LABELED PROLIFT+M DEVICE TO PHYSICIANS INTENDED FOR PERMANENT IMPLANTATION IN PATIENTS

62. The FDA's 510(k) process by which Prolift and Prolift +M were cleared for sale in the United States by Ethicon admittedly has limitations, however, it was never intended that FDA's reviewer in completion of a 90-day review of a written 510(k) submission designed and authored by Ethicon could independently determine the accuracy and completeness of the information given to it by Ethicon. The FDA's reviewers, primarily without clinical experience or training, do not have a role to handle, test or use Ethicon's proposed new device nor does anyone at the FDA have a role to conduct independent laboratory testing or clinical trials in patients as part of its 510(k) clearance process. It is an Ethicon employee required by FDA to sign a "Truthful and Accuracy Statement" in the 510(k) certifying Ethicon has provided FDA with all material information about the proposed product in the

[16] Institute of Medicine (IOM), *Medical Devices and the Public Health: The FDA 510(k) Clearance Process at 35 years*, Washington, DC: National Academies Press, 2011, available at: http://www.nap.edu/catalog.php?record_id=13150. (last visited July 14, 2015).

[17] *See* U.S. Government Accountability Office, *Medical Devices: FDA Should Tae Steps to Ensure that High-Risk Device Types are Approved through the Most Stringent Premarket Review Process*, January 2009, available at: http://www.gao.gov/assets/290/284882.pdf (last visited July 15, 2015); *see also* DM Zuckerman et al., *Medical Device Recalls and the FDA Approval Process*, 171(11) Archives of Internal Medicine 1006-1011 (2011); JZ Hines et al., *Left to Their Own Devices: Breakdowns in United States Medical Premarket Review*, 7(7) Public Library of Science Medicine e1000280 (2010); Public Citizen, *Substantially Unsafe: Medical Devices Pose Great Threat to Patients; Safeguards must be Strengthened not Weakened, February 2012*, available at: http://www.citizen.org/documents/substantially-unsafe-medical-device-report.pdf (last visited July 15, 2015).

510(k). Without the presence of an Ethicon signed Truthful and Accuracy Statement, and Ethicon 510(k) application cannot be even filed by FDA for future review.

63. The FDA's reviewer in ODE's surgical devices branch, assigned the task to complete a 510(k) submission review within 90 days, must rely on Ethicon's Truthful and Accuracy certification, as well as Ethicon's knowledge and experience as the expert and designer of both Prolift and Prolift+M and other similar products to be willing and able to provide FDA with adequate and complete disclosure about the device it intends to market. FDA must assume that Ethicon intends to sell a safe and effective product for implantation in patients in the United States. The FDA reviewer is also aware that it is a Prohibited Act (21 U.S.C. §331(a)(b)) for Ethicon to sell a medical device in the United States that is not safe, effective and adequately labeled. As part of the 510(k) process, Ethicon's commitment to adherence to Quality Systems must only be assumed by FDA's ODE reviewer, since that information is not required to be provided by Ethicon in the 510(k), nor is it required to be reviewed or verified at time of FDA's review of the 510(k). Therefore, despite obtaining 510(k) clearance from FDA, it remains Ethicon's non-delegable duty (not the FDA's) to ensure the device it manufactures and commercially markets actually performs as it described to FDA and was cleared by its 510(k) when implanted in a patient. It is Ethicon's role (not the FDA's) to ensure that there are no new unaddressed issues of safety and effectiveness for the commercial product which would render its product adulterated and misbranded. If Ethicon knows that the Prolift/Prolift+M devices do not perform as described to FDA and cleared by the 510(k) (K071512) after May 15, 2008 as Total, Anterior and Posterior Pelvic Floor Repair Systems, then Ethicon (not the FDA) is selling a misbranded and adulterated product(s). Ethicon's commercial product must legally perform as described and cleared by its 510(k).

64. The 510(k) process review hinges on the meaning of a product's 'intended use'. For example, Ethicon changed the intended use of its 510(k) cleared Gynecare Prolene Soft Mesh (K013718) from synthetic surgical mesh intended for hernia repair when it created pre-shaped mesh designed for use in the pelvic floor repair (PFR) and created new specially designed insertion tools for a PFR procedure kit. Ethicon created a new POP mesh kit intended for pelvic organ prolapse (POP) repair, which was not consistent with its clearance and intended use of Gynecare Prolene Soft mesh. It was the same PS mesh, but with a new intended use which introduced new issues of safety and effectiveness for PFR not seen with simple sheets of surgical mesh intended for hernia repair. The new intended use for PROLIFT first required clearance of a new 510(k) by FDA for marketing with Ethicon providing a legally marketed predicate for the same intended use (POP) so it could be cleared by a 510(k). The change in intended use also required Ethicon to provide an adequate prescription label to physicians as well as adequate instructions and training for POP as well as warnings and precautions. FDA's 21 C.F.R. § 801.4 Meaning of "intended use".

65. The words intended uses or words of similar import in §§ 801.5, 801.119, and 801.122 refer to the objective intent of the persons legally responsible for the labeling of devices. The intent is determined by such persons` expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for

example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he received the devices, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses. But if a manufacturer knows, or has knowledge of facts that would give him notice that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a device which accords with such other uses to which the article is to be put.

## III. OVERVIEW OF MY ROLE AS AN FDA REGULATORY EXPERT

67. I view my primary role as an FDA regulatory expert in this litigation as providing a regulatory discussion of the FDA's and medical device manufacturer's framework as it relates to the Federal Food Drug and Cosmetic Act (the Act), implementing regulations, FDA, industry and the public. This discussion is supported by my own training, experience and history of activities both at FDA and after FDA. Congress by passage of the Medical Device Amendments of 1976 to the Act assigned FDA a specific role to be the public's gatekeeper controlling the entry of medical devices into the United States. The FDA was charged to develop necessary regulations and frameworks for industry to use to bring new medical devices to market for the use of the public and to facilitate that the devices were adequately designed, manufactured, monitored and labeled. Congress placed limitations on the reach of FDA's authority, and as a government agency the FDA has practical restrictions placed on its funding and resource allotment. Congress placed the primary responsibility for ensuring compliance with the Act not on the FDA but on each medical device manufacturer, the entity engaged and profiting from the successful design, manufacture, distribution monitoring and sale of its medical devices. All United States medical device manufacturers are required to establish and adhere to internal methods for ensuring compliance with the Act and implementing regulations. Each medical device manufacturer is required to create and adhere to its own standard operating procedures (SOP) for product design, manufacturing, oversight, reporting, record keeping, failure investigation with the ultimate goal to ensure it sells safe and effective medical devices, will voluntarily update labels and marketing and take steps to protect the public from harm. It is a 'Prohibited Act' for any medical device manufacturer, including Ethicon and Johnson & Johnson, to sell medical devices in the United States that are not safe, effective, adequately designed, manufactured and labeled and in full compliance with the Act. (21 U.S.C. § 331(a)(b)).

68. The first area of my anticipated testimony will include, but not be limited to, general discussion of FDA's overall mission to protect the public; its history of reliance on a risk-based device classification paradigm as well as to describe pertinent regulatory terms for Prolift/Prolift+M such as:'510(k)', 'IDE', 'PMA', 'clinical trials', preclinical', 'IRB', 'adequate informed consent', 'foreign data', 'label', 'marketing', 'new claims', 'intended

use', 'substantial equivalence (SE)', 'not substantially equivalent (NSE)', 'safety and effectiveness', 'raising new issues of safety and effectiveness', 'review clock', 'Class III', 'investigational', 'note to file', 'clearance', 'approval', 'Quality Systems', 'Good Manufacturing Practices', 'Medical Device Reporting'(MDR), 'FDA Advisory Committees (AdCom)', 'predicate', 'post-market surveillance', '522 Order', 'reclassification', 'safety signal', 'warning', 'precaution', 'instructions for use', failure effects mode analysis (FEMA), 'risk management', 'failure investigation', 'corrective and preventive action (CAPA)', 'design', 'complaint', Medical Device User Fee Amendment (MDUFA), 'regulatory hold', 'health risk', 'supplement', 'Dear Health Care Provider Letter', and 'off-label'. I will describe the role of various Offices in FDA's Center for Devices and Radiological Health (CDRH) as well as members of Office of Device Evaluation (ODE), 510(k) reviewers, the standard used by FDA's reviewers to consider clearance and the procedure and completion of a 510(k) Determination Flow sheet as part of the official 510(k) record to support FDA's decision making. Other general issues which may be covered and as related to TVM POP and Prolift +M include FDA's general use of compliance and enforcement actions, and enforcement discretion including Warning Letters, FDA facility inspections, observations listed in FDA Form 483, and the differences between mandatory versus voluntary recalls; FDA's reliance on issuance of public notifications as an expedient regulatory action (tool); medical device safety and efficacy as applicable to industry standards and quality systems; pre- and post-market regulatory requirements in terms of adequate study, design, comparison to predicates, introduction and disclosure of new issues of safety and effectiveness, the limitations of 510(k) clearance and duties for commercial marketing applicable to all medical device manufacturers; FDA's ability to reach out directly to health care providers and patients using vehicles such as Public Health Notifications and Safety Alerts to warn about the potential risks of devices including lack of long-term safety and efficacy data; FDA's ability to use public FDA Advisory Committee meetings for publicity and to solicit outside expert opinions about issues, for example the use of TVM for SUI and POP products; FDA's use of reclassification of devices based on new risk concerns or new benefits and controls; FDA's ability to reclassify previously exempted products to require clearance of a 510(k); FDA's authority to issue a 522 Order to require a Sponsor (or an entire industry) to conduct studies to obtain post-market safety and efficacy information.

69. Whenever feasible, the discussion will be focused on regulatory issues relevant to Prolift/Prolift+M as well as Gynecare Prolene Soft (PS) mesh (K013718; K071512). The Prolift and Prolift+M 510(k) includes a need to discuss the history of FDA's determination that, despite Ethicon's years of aggressive off-label marketing of Prolift to surgeons for TVM POP, Ethicon's employees had erred when incorrectly decided Prolift could be marketed as a TVM POP system as a modification of Gynecare PS mesh (K013718) without clearance of a 510(k). FDA's documents show that it conveyed to Ethicon the need for Prolift 510(k) clearance for marketing in the United States. For Ethicon to obtain 510(k) clearance of Prolift, FDA's documents show that the Agency allowed Ethicon to add Prolift to its current Prolift+M 510(k), but FDA required Ethicon to provide a predicate for both Prolift and Prolift+M for TVM POP. Ethicon was also requested by FDA to update the 510(k) with all patient experience information from use of Prolift in patients.

70. The Prolift/Prolift+M 510(k) was updated by Ethicon following inclusion of Prolift, to cite as TVM POP predicates competitor's American Medical Systems (AMS) Apogee Vault Suspension PFR Kit (K040537)(cleared April 22, 2004) and Perigee Posterior and Apical PFR Kit (K040623) (cleared May 17, 2004). Both of the AMS predicates were cleared as transvaginal mesh (TVM) for pelvic floor repair (PFR) and POP Kits. Other predicates and 510(k) clearances cited by Ethicon as support of an established acceptable implant history of Prolift and Prolift+M as long-term implants in patients included: Gynecare Prolene Soft (PS) Mesh; UltraPro Mesh; Prolene Mesh; and Monocryl and Prolene suture. For Ethicon's Prolift/Prolift+M 510(k)'s, Ethicon at all times was considered by FDA as the knowledgeable expert for its product. In the role of expert, Ethicon had a non-delegable duty to comply with all pre- and post-market regulatory requirements including providing 'truthful and accurate' information to FDA's reviewers, ensuring adequacy and accuracy of each section contained in Ethicon's 510(k) application as well as each of the related supplements. Ethicon was required to provide full description of risk information to FDA and physicians including for the predicates, discussed in the medical literature, history of similar products and for the proposed intended use. My Ethicon Prolift/Prolift+M discussion will also require of marketing the instructions for use, patient brochures, professional education materials, sales materials, advertising and role of Ethicon's sales force and designated key opinion leaders (KOL).

71. As it is required, there will be more general discussions of the history and evolution of each of Ethicon's relevant synthetic surgical meshes (Prolene[18], GyneCare PS, UltraPro, Gynecare M) and sutures ( Prolene, Monocryl) and Ethicon's use of transvaginal synthetic mesh for new indications in the female pelvis as tapes used to treat stress urinary incontinence (SUI) and systems for Prolift/Prolift+M pelvic organ prolapse (POP) and pelvic floor repair.

72. As a regulatory consultant, and as requested, I will provide regulatory overviews of the United States history and evolution of Ethicon's (SUI) and (POP) products including its reliance on FDA's Guidances, including the FDA's Surgical Mesh Guidance, pelvic industry predicates, global industry standards and marketing claims to physicians and requirement for Ethicon to balance benefit claims with risk information; the history of Monocryl as an absorbable suture and then its adaptation by Ethicon to create a partially absorbable mesh; FDA's required use of the "Least Burdensome method" for industry and Ethicon's ability as the knowledgeable expert to reference (bridge) information already contained in its prior cleared and approved marketing applications in lieu of conducting duplicate testing; FDA's requirements for Ethicon to obtain clearance of 510(k)s before start of marketing and then to continue to market the product that was cleared by the FDA in the 510(k) in the United States; Ethicon's creation and implementation of internal standard operating procedures (SOP) to develop, design, test, manufacture and control Prolift/Prolift+M medical devices for POP based on Ethicon's use of FDA's minimal Quality Systems Regulations (QSR) (21 C.F.R. 820); the evidence that supports my expert opinions about Ethicon's adherence (or lack of adherence) to accepted methods for industry design and risk management; examples of Ethicon's evidence of risk management procedures for Prolift/Prolift+M including

[18] Ethicon's Prolene™- first used in commerce by Ethicon and Trade Marked for Prolene Sutures in 1968; first used and Trade Marked for Prolene Surgical Mesh in 1975.

postmarket surveillance, monitoring, complaint handling, failure investigation, medical device reports (MDRs), statistical trending, identification and completion of adequate corrective and preventive actions (CAPA); Ethicon's continuing ability and duty to update its own product labels, marketing and salesforce for surgeons and women to provide adequate risk information and warnings; Ethicon's duty to provide prescribers with adequate prescription labels and surgical training as well as its duty to train and update its own salesforce; Ethicon's history of interactions with FDA and physicians regarding risks and benefits of Prolift/Prolift+M; Ethicon's continuing ability to ensure its own compliance with the Act and voluntarily update its own labeling, salesforce, marketing; Ethicon's ability to discontinue sales or voluntarily withdraw and/or recall Prolift/ Prolift+M from the United States market. The global industry standards and my professional experience and training provide a substantial foundation for the bases of my opinions.

73. In terms of the history of interactions between FDA and Ethicon for TVM, POP and SUI, as required I will provide a discussion of FDA's use of notification processes and/or public statements concerning spreading concern about potential risks of TVM for POP and SUI; the history of FDA's Advisory Committee Panel and conclusions for Trans-Vaginal Tape (TVT) for SUI and TVM for POP; FDA's issuance of 522 orders to Ethicon as well as the TVM industry to specifically obtain post-market safety and efficacy information for POP and Prolift/ Prolift+M implanted in women; Ethicon's decision to opt to voluntarily stop selling (de-commercialize) Prolift and Prolift +M in lieu of fulfilling FDA's request it obtain post-market safety and efficacy information for its POP products implanted in women.

74. Additionally, I may provide discussion regarding relevant regulatory matters relating to Prolift/Prolift +M as discussed in my expert report(s) and/or disclosures in *this case and previous cases* and thirteen opinions. I may also respond to testimony and opinions of Defendant's experts within my subject matter expertise. For a specific plaintiff, I will attempt to limit my discussions and opinions to the timeframe appropriate to the patient's implantation and when relevant to explant. I will testify that all my expert opinions are made to a reasonable degree of regulatory, professional and medical certainty.

## IV. OPINIONS

### 1. OPINION #1: ETHICON'S DOCUMENTS AND ACTIONS HAVE DEMONSTRATED A CORPORATE WILLINGNESS TO PERMANENTLY IMPLANT INVESTIGATIONAL NEW MEDICAL DEVICES IN AMERICAN WOMEN BEFORE OBTAINING 510(k) CLEARANCE AND WITHOUT ADHERING TO SAFEGUARDS ESTABLISHED FOR CONDUCTING ETHICAL MEDICAL RESEARCH.

**Applicable Regulations:** 21 C.F.R. § 807; 21 U.S.C. § 351(a); 21 C.F.R. § 812; 21 C.F.R. § 814; 21 U.S.C. § 352(a) (f)(1)(2) & (t); 21 U.S.C. § 321(n); 21 U.S.C. § 331(a)(b); 21 C.F.R. §50; 21 C.F.R. § 56

2. **OPINION # 2: ETHICON MARKETED PROLIFT PROCEDURE KITS IN THE UNITED STATES FOR TVM POP BEFORE ADEQUATE STUDY, DESIGN OR TESTING AND WITHOUT FDA'S 510(K) CLEARANCE. ETHICON MARKETED BOTH PROLIFT/PROLIFT+M FOR TVM POP WITHOUT A COMMITMENT TO CONDUCT ROBUST POST-MARKET SURVEILLANCE. AS A RESULT OF ETHICON'S ACTIONS, PROLIFT/PROLIFT+M WERE MARKETED TO SURGEONS THROUGH ITS OWN SALESFORCE FOR TVM POP WITH INADEQUATE INSTRUCTIONS FOR USE AND WARNINGS**

   **Applicable Regulations**: 21 C.F.R. § 807; 21 U.S.C. § 351(a); 21 C.F.R. § 812; 21 C.F.R. § 814; 21 U.S.C. § 352(a)(f)(1)(2)(t); 21 U.S.C. § 321(n); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 801.109; 21 C.F.R. § 820; 21 C.F.R. § 801.4 [19]

3. **OPINION #3: ETHICON'S PROLIFT/PROLIFT +M 510(K) FAILED TO ADEQUATELY DESCRIBE TO FDA THE RISKS AND DIFFICULTIES REPORTED WHEN PROLIFT WAS IMPLANTED FOR TVM POP IN WOMEN.**

   **Applicable Regulations**: 21 C.F.R. § 807; 21 C.F.R. § 812; 21 U.S.C. § 352(a)(f)(1)(2),(t); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 801.109.

4. **OPINION #4: ETHICON'S SEPTEMBER 20, 2007 RESPONSE TO FDA DID NOT CONCUR WITH FDA'S AUGUST 24, 2007 REQUESTS FOR THE PROLIFT/PROLIFT+M 510(K) NOR DID ETHICON FULLY DISCLOSE RISKS TO FDA.**

   **Applicable Regulations**: 21 C.F.R. § 807; 21 U.S.C. § 812; 21 U.S.C. § 352(a)(f)(1)(2),(t); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 801.109

5. **OPINION # 5: ETHICON MODIFIED THE MANDATORY 21 C.F.R. § 807.87(k) 510(k) TRUTHFUL AND ACCURACY STATEMENT'S WORDING WITHOUT ANY DISCLOSURE OF THE CHANGES TO FDA'S REVIEWER.**

   **Applicable Regulations**: 21 C.F.R. § 807.87(k); 21 U.S.C. § 352(t); 21 U.S.C. § 331(a)(b); 18 U.S.C. § 1001

6. **OPINION #6: ETHICON'S ACTIONS WITH PROLIFT+M CONTRIBUTED TO ITS MARKETING OF MISBRANDED PROLIFT+M PFR KIT WITH INADEQUATE TESTING, INSTRUCTIONS FOR USE AND WARNINGS.**

   **Applicable Regulations**: 21 U.S.C. § 352(a)(f)(1)(2); 21 U.S.C. § 321(n); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 801.109.

[19] There are also a number of industry standards that support each of my opinions. For brevity, I have listed these in my reliance list.

7. **OPINION # 7: ETHICON DID NOT VOLUNTARILY UPDATE AND TIMELY CIRCULATE PROLIFT/PROLIFT+M LABELS TO PHYSICIANS WHICH FULLY NOTIFIED THEM OF CHANGES REQUESTED BY THE FDA.**

   **Applicable Regulations**: 21 C.F.R. § 807; 21 U.S.C. § 352(a)(f)(1)(2); 21 U.S.C. § 321(n); 21 U.S.C. § 331(a)(b); 21 C.F.R.§ 801.109; 21 C.F.R. § 820.

8. **OPINION #8: ETHICON CONTINUED TO MARKET PROLIFT WITH AN INACCUARATE AND MISLEADING LABEL WHEN IT DID NOT IMPLEMENT AND CIRCULATE OR NOTIFY SURGEONS ABOUT CHANGES IN THE CLEARED FINAL LABEL UNTIL LATER IN 2009.**

   **Applicable Regulations**: 21 C.F.R. § 807; 21 U.S.C. § 352(a)(f)(1)(2); 21 U.S.C. § 321(n); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 801.109; 21 C.F.R. § 820.

9. **OPINION #9: ETHICON MARKETED PROLIFT SYSTEMS WITHOUT ADEQUATE STUDY, TESTING OR FOLLOW-UP TO LEARN THE CLINICAL '*CONSEQUENCES*' FOR PATIENTS OF MANUFACTURING CHANGES INTRODUCED FOR PROLIFT/ PROLIFT +M SYSTEMS.**

   **Applicable Regulations**: 21 C.F.R. § 807; 21 C.F.R. § 820.30; 21 C.F.R. § 820.70; 21 C.F.R. § 801.109; 21 C.F.R. § 812

10. **OPINION #10: ETHICON'S MARKETING FAILED TO WARN PHYSICIANS THAT IT HAD NOT STUDIED THE SHORT- AND LONG-TERM RISKS, CHANGES IN TISSUE INGROWTH, PROPERTIES OF HEALING, INFLAMMATION, NAMELY "*CLINICAL CONSEQUENCES*" FOR WOMEN OF THE AMOUNTS OF ABSORBABLE POLIGLECAPRONE IMPLANTED BY PROLIFT+M MESH DURING PFR.**

    **Applicable Regulations**: 21 C.F.R. § 820.30; 21 U.S.C. § 352(a)(f)(1)(2); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 801.109; 21 C.F.R. § 820.20; 21 C.F.R. § 820.25. 21 C.F.R. § 812; 21 C.F.R. § 50

11. **OPINION # 11: ETHICON DID NOT DISCLOSE TO FDA THAT ETHICON'S 'LIGHTNING PROJECT' WAS MARKETING'S PLANS TO MAKE UNSUPPORTED CLAIMS OF 'SUPERIORITY' FOR PROLIFT+M AS A 'LIGHTER' MESH TO DRIVE OBSOLESENCE OF PROLIFT FOR POP IN TWO YEARS.**

    **Applicable Regulations**: 21 C.F.R. § 807; 21 C.F.R. § 801.109; 21 C.F.R. § 1.21

12. **OPINION #12: ETHICON WAS OFFICIALLY TOLD BY FDA'S ODE IT MARKETED MISBRANDED AND ADULTERATED PROLIFT KITS WHEN IT BEGAN SALES IN THE UNITED STATES WITHOUT 510(K) CLEARANCE FOR TVM POP. ETHICON WAS TOLD BY FDA THAT CONTINUED MARKETING OF PROLIFT FOR TVM POP BEFORE 510(K) CLEARANCE OR OUTSIDE AN FDA APPROVED IDE (AUGUST 24, 2007 THROUGH MAY 15, 2008) DID NOT COMPLY WITH THE ACT. YET, AT NO TIME UP THROUGH MAY 15, 2008 DID ETHICON EVER INFORM SURGEONS AND WOMEN THAT ETHICON PROMOTED PROLIFT FOR TVM POP, AN INVESTIGATIONAL PRODUCT, OFF LABEL AND WITHOUT FDA'S PRE-MARKETING CLEARANCE.**

**Applicable Regulations**: 21 U.S.C. § 352(a)(f)(1)(2)(t); 21 U.S.C. § 321(n); 21 U.S.C. § 331(a)(b); 21 U.S.C. § 351; 21 C.F.R. § 807; 21 U.S.C. § 360e

13. **OPINION #13: ETHICON'S DECISION TO STOP ALL SALES OF PROLIFT/PROLIFT+M (DE-COMMERCIALIZE) STOPPED ALL ETHICON'S EFFORTS TO COMPLY WITH FDA'S 522 ORDER. ETHICON'S MANAGEMENT CHOSE TO DISCONTINUE SALES OF PROLIFT+M RATHER THAN OBTAIN SCIENTIFIC POST-MARKET SAFETY AND PERFORMANCE INFORMATION ABOUT THE PRODUCT FOR FDA, PHYSICIANS AND PATIENTS.**

**Applicable Regulations**: 21 C.F.R. § 820.198; 21 C.F.R. § 820.250; 21 C.F.R. § 803; 21 C.F.R. § 820.100; U.S.C. § 352(a)(f)(1)(2); 21 U.S.C. § 321(n); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 801.109; 21 C.F.R. § 822.3(j); 21 U.S.C. § 360l

## V. SIGNATURE

75. I reserve the right to amend or supplement this report and opinions in the event that additional pertinent information becomes available or additional issues are raised in reports of other experts.

Suzanne Parisian, M.D.

Suzanne Parisian, M.D.

1-30-2016

Date

76. Each of the thirteen opinions is discussed individually below along with the bases supporting the opinion.

## VI. OPINION #1:

ETHICON'S DOCUMENTS AND ACTIONS HAVE DEMONSTRATED A CORPORATE WILLINGNESS TO PERMANENTLY IMPLANT INVESTIGATIONAL NEW MEDICAL DEVICES IN AMERICAN WOMEN BEFORE OBTAINING 510(k) CLEARANCE AND WITHOUT ADHERING TO SAFEGUARDS ESTABLISHED FOR CONDUCTING ETHICAL MEDICAL RESEARCH.

**Applicable Regulations:** 21 C.F.R. § 807; 21 U.S.C. § 351(a); 21 C.F.R. § 812; 21 C.F.R. § 814; 21 U.S.C. § 352(a) (f)(1)(2) & (t); 21 U.S.C. § 321(n); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 50; 21 C.F.R. § 56

77. (Johnson & Johnson) Ethicon has knowingly engaged in marketing of new investigational devices to United States physicians, including Prolift, without first obtaining pre-marketing clearance from FDA, or without adherence to patient safeguards such as occur in the FDA approved Investigational Device Exemption (IDE) for ethically collecting human data. Ethicon also failed to adequately update the FDA on the risks of its Prolift/Prolift+M products in its marketing application. Ethicon has engaged in this pattern of violative behavior without formal regulatory actions taken by the FDA's ODE staff. However, Ethicon's actions, with or without regulatory action by FDA's ODE staff, are clearly prohibited by the Act for all medical device manufacturers and constitutes Ethicon marketing adulterated and misbranded devices.

78. One example relevant to Ethicon's conduct for POP and the 'Prolift+M' was Ethicon's off-label promotion of Gynecare PROLIFT to physicians for POP beginning in 2004. Gynecare Prolene Soft (PS) Mesh (K013718) was cleared by FDA intended for hernia repair. Surgical mesh is a pre-Amendments device which was classified as Class II in 1988. Beginning in 1992. FDA cleared 510(k)s for surgical mesh indicated for POP repair under general surgical mesh. Ethicon changed the intended use to a mesh for POP to TVM without first obtaining clinical data with an IDE or informing physicians or implanted women that the product had not been cleared or approved by the FDA for POP.

79. Ethicon had made a series of significant changes to its cleared Gynecare Prolene Soft Mesh without submission of a new 510(k) and giving FDA an opportunity to review a procedure kit it intended to market with pre-cut PS mesh and insertion tools for POP. Ethicon was essentially marketing an 'investigational device' for POP calling it a minor modification of its already cleared Gynecare Prolene Soft (PS) Mesh for hernia repair. It did this without the safeguards of collecting data in the United States with an approved IDE, or outside the United States with patients giving signed informed consent to participate as subjects in Ethicon's clinical trials. Ethicon developed pre-cut mesh shapes intended for PFR and POP as well as POP insertion tools all to be marketed as part of a Prolift procedural kit.

80. When Ethicon submitted a 510(k) to market Prolift+M for Total, Anterior and Posterior Pelvic Floor Repair it cited as a predicate PROLIFT (K013718), a product without a 510(k) clearance for POP, as a suitable POP predicate for Prolift+M. FDA was merely told that the

"PROLIFT Systems consisted of a shape change to the currently marketed Gynecare Gynemesh PS as well as addition of inserter tools to create a procedural kit." FDA requested Ethicon's rationale for the "Insignificant change" from Gynemesh PS to the Prolift Device: K071512 S01. However, as of August 7, 2007, Ethicon was on official notice from FDA ODE that its Prolift could not be legally marketed until it had clearance of a 510(k). Ethicon would need to identify a suitable predicate for 510(k) clearance of both Prolift and Prolift+M kit for POP before marketing. Eleven years later, in 2012, after FDA became involved in transvaginal mesh safety issues with the industry, the Gynecare Prolene Soft mesh (K013718) 510(k) indication was changed from a mesh for hernia repair to for POP as PROLIFT for a new indication.

81. The United States **Gynecare Prolift** trademark, which is not required to be submitted to the FDA in a 510(k), was first filed by Johnson & Johnson on September 22, 2004. The application listed the first commercial use of Gynecare PROLIFT in the United States as a 'general surgical mesh' on March 10, 2005.

82. In a response to the FDA in 2012 regarding the FDA's 522 order, Ethicon told the Agency that in 2008, it sold 17,882 PROLIFT kits and 0 PROLIFT+M kits. (K071512 was cleared May 15, 2008)[20] There is no information provided about PROLIFT sales prior to 2008.

83. Clearance of GYNEMESH PROLENE Soft (Polypropylene) Mesh in January 8, 2002- FDA assigned product Code FTL has no mention of use of PS mesh in the pelvis:

> *This mesh is intended for repair of hernia or other fascial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result.*

84. Ethicon decided to subsequently de-commercialize PROLIFT as transvaginal insertion of mesh procedure kit for POP (K071512) rather than complete the FDA's 522 Order study for obtaining post-market safety and efficacy data. As a result the intended use for GYNEMESH PROLENE Soft (POLYPROPYLENE) Mesh (K013718), the product used off-label in PROLIFT until its first clearance in May 2008 was subsequently changed to the following clearance in September 28, 2012 – FDA assigned Product Code OTO:

> *GYNECARE PROLENE Soft (Polypropylene) Mesh is indicated for tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor in vaginal wall prolapse where surgical treatment is intended, either as mechanical support or bridging material for the fascial defect.*

85. The Prolift trademark was made dead by Johnson & Johnson as of May 31, 2013.

86. FDA views manufacturers (sponsors) as the entity legally responsible for monitoring the conduct of its clinical investigators while engaged in clinical studies intended for support of future marketing applications. FDA requires manufacturers to ensure adequate control and

[20] ETH.MESH.07724600

accountability of investigational products provided to clinical investigators. FDA requires manufactures to ensure that physician investigators obtain documentation of informed consent prior to enrollment of any subject in a study and maintain reports. The same is true for studies conducted under funding by all government agencies.

87. In September 2011, FDA held an Advisory Committee Panel meeting to discuss surgical mesh used for transvaginal POP repair. The panel members of experts discussed the number of serious adverse events associated with use of surgical mesh for TVM POP. The Panel's consensus was that the safety of surgical mesh for TVM POP repair was not well established and that, depending on the compartment, vaginal placement of the mesh for POP repair may not be more effective than traditional "native-tissue" repair without mesh. As such the Panel concluded that the risk/benefit profile of surgical mesh for TVM POP repair is not well-established and recommended that the devices be reclassified by FDA from Class II to Class III.

88. FDA published its proposed order to reclassify surgical mesh for TVM POP from Class II to Class III in the Federal Register of May 1, 2014.[21] The FDA then issued a Final Order on January 5, 2016 "Effective Date of Requirements for Premarket Approval of Surgical Mesh for Transvaginal Pelvic Organ Prolapse Repair" indicating it decided to reclassify surgical mesh as "high risk" to Class III and would require PMA approval (or PDP completion) by July 5, 2018 for TVM POP devices cleared based on pre-Amendments general surgical mesh devices. FDA also would convene a Panel meeting on February 26, 2016 to discuss reclassification of the surgical insertion instruments currently described under 21 C.F.R. 876.4730 "Manual Gastroenterology-Urology Surgical Instrument and Accessories" prior to completing finalizing of reclassification from Class I (exempt) to Class II requiring a 510(k) clearance. When these instruments are packaged together for the purpose of TVM POP as a kit, another 510(k) is required for the instrumentation. Manufacturers will have the future option to include the instruments in a PMA submission for convenience.

89. FDA wrote in January 2016 that it still was not aware of any new information since the 2011 Panel meeting that would provide a basis for a different recommendation. To justify the risk of TVM for POP, the FDA has cited having received thousands of reports that demonstrated the wide spectrum of significant complications for women associated with TVM implantation for POP. The FDA proposed reclassification for TVM mesh used for POP based on risk. The reclassification would require companies wishing to continue marketing these products commercially in the United States to submit a new PMA application (or complete a PDP) within 30 months to obtain FDA's approval. The PMA application for FDA approval must demonstrate the safety and effectiveness of the implant for TVM POP as well as the manufacturing controls required to ensure the products remain safe and effective. The TVM POP products without PMA approval after the specified date for approval can no longer be marketed in the United States and are not to be available to physicians in the United States outside an approved IDE.

90. Under the FDA's final order a PMA for surgical mesh for TVM POP repair is required to be filed on or before July 5, 2018 for any pre-Amendments (genera surgical mesh) related Class

[21] 79 F.R. 24634; 79 F.R. 24642.

III devices in commercial distribution before May 28, 1976 (or found substantially equivalent to a pre-amendments device) on or before July 5, 2018. Any other TVM POP device subject to this order is required to have an approved PMA in effect before it can begin marketing. A similar situation for the FDA with reclassification from Class II to Class III based on risk was the FDA's handling of silicone breast implants.

91. To ensure compliance with the Act, manufacturers such as Ethicon also conduct voluntary product recalls to prevent violative "off label" use by physicians based on public health safety and the manufacturer's legal requirement under the FDCA to provide adequate instructions for safe and effective use per 21 C.F.R. §801.4 when learning of a new intended use. As an example, in April 2004, Johnson & Johnson, Ethicon (not the FDA), conducted a voluntary recall of its Precise Rx Biliary Stents. This recall action was classified by FDA as a Class I Recall (highest potential public health risk). The Precise Rx Biliary Stent is a class II device cleared by 510(k) for Ethicon as a biliary stent based only on mechanical (bench) testing with no requirements for clinical testing. The recall was conducted by J&J because the firm "became aware" of "off label" use by physicians for a new intended use. Also, Ethicon became aware the new off label use was as a vascular stent (a Class III device) which was prohibited by the 510(k) clearance. Vascular stents, unlike biliary stents, are PMA approved products which require a firm first to provide and obtain FDA's approval of clinical data and manufacturing data and a label as a PMA that can support safety and efficacy. The recall by Johnson & Johnson followed FDA's Office of Compliance (OC) (post-market staff) and Ethicon's both "becoming aware" of "off label" use of the product which had resulted in patient injuries. Johnson & Johnson voluntarily opted to remove all its violative products (bile stents) from the United States market, filed a 510(k) submission with FDA to change the product's labeling and sent out a Dear Doctor letter to notify physicians that "off-label" use of its biliary stent was not safe nor effective as a vascular stent.

92. The reason off-label promotion by manufacturers is not permitted by the Act and in the United States, outside the confines of the FDA approved IDE or before 510(k) clearance is that, from a practical point the Sponsor, in this case Ethicon, when engaged in off label marketing has already obtained the desired commercial market, namely the vascular stent market (or for Prolift the TVM POP market). Once successfully selling the product to United States physicians for patient use, there is less incentive for Ethicon to perform the necessary research, development and testing studies to ensure safety and efficacy or develop the warnings and instructions for use (IFU) in a formal manner to provide to physicians and patients. From a practical perspective, the commercial horse has already left the regulatory barn if off-label use is permitted. In terms of conducting ethical research under an FDA approved IDE, there is effort involved for obtaining and adhering to an IDE, including the need for reporting and patient outcome accountability. As with Prolift's marketing for TVM and POP, when conducted without an IDE, patient outcomes and risk information can easily be lost. For a new product, for example Prolift, the sponsor may use the patient information from the off-label use to attempt to redesign a product and obtain later clearance of an 'improved' or "modified" next generation product (i.e. Prolift+M). However, all the earlier patient data can be lost, missing or not tabulated and the implanted patients (and even the physicians as clinical investigators) were not adequately informed they were 'subjects' in a

manufacturer's medical device study and used essentially for the purpose of research, often receiving an early prototype (first generation) device. With such an approach by industry, regulatory agencies like the FDA and physicians and patients will not be informed of the product risks. The company essentially gains information from encouraging United States physicians use their own patients essentially as Guinea pigs to conduct the company's product research.

93. As an example to support that a commercial product sold must perform like its cleared 510(k) there is also a Johnson & Johnson example. However, this time it is the Johnson & Johnson's company LifeScan. J&J had multiple 510(k) clearances from an ODE division to sell its blood glucose meter SURESTEP (K942455; K971014; K970556; K984261; K022724; K023194; K023832). However, the ODE reviewer was not informed by J&J in the 510(k)s that its glucose meters did not perform commercially as cleared in the 510(k)s through 1999 and there had been reports of patient injuries and deaths. Johnson & Johnson/LifeScan had a $45 million class action settlement in December 2001 with purchasers of the defective SureStep blood glucose meters.[22] Johnson & Johnson's public statement issued on its LifeScan's SureStep Meter December 15, 2001:

> *LifeScan, Inc. a Johnson & Johnson (NYSE:JNJ) company, today entered a plea of guilty to three misdemeanor charges related to a federal government investigation of its SURESTEP Blood Glucose Meter. LifeScan will pay a fine of $29.4 million and an additional $30.6 million in civil settlement to the government.*
> *This plea ends a three-year government investigation of the way LifeScan addressed two problems associated with the SURESTEP product in 1997…*
> *Through this settlement, LifeScan acknowledges introducing an adulterated and misbranded medical device; failing to provide appropriate notifications and information to the U.S. Food and Drug Administration (FDA), and submitting false and misleading reports to the FDA.*
> *…LifeScan admits that the SURESTEP product labeling was deficient that the company did not properly notify the government of those deficiencies as was slow to remedy them completely.*
> *"Mistakes and misjudgments were made" said Ralph S. Larsen, Chairman and Chief Executive Officer of Johnson & Johnson...*[23]

94. As not discussed in J&J's Statement issued about LifeScan and SureStep, the FDA was not the entity that identified or even brought the initial action against the 510(k) LifeScan SureStep for marketing a misbranded and adulterated 510(k) cleared product. The FDA's pre-market ODE reviewers had continued clearing 510(k)s for J&J to market its SureStep

[22] The Gray sheet LifeScan $45 Mil. Glucose Meter Settlement Approval hearing Set for Dec. 10 Posted December 3, 2001 Article # 01270490017.

[23] Johnson & Johnson Statement on LifeScan's SURESTEP Meter, available at http://files.shareholder.com/downloads/JNJ/0x0x52155/ed79019f-e7a0-49b1-a9ba-fef.pdf (last visited January 19, 2016).

based on J&J's assurances of adequate performance. ODE reviewers looking at the pre-market applications did not question J&J to ascertain the acceptable post-market performance nor dose ODE look at the post-market Medical Device report (MDR) database or the medical literature to identify 'post-market" risk.

95. The regulatory action against Johnson & Johnson for the SureStep was a *qui tam* successfully brought by two LifeScan relators. Robert Konrad, M.D. a clinical pathologist and a John Pumphrey a chemist, both employees of LifeScan involved in Advanced Reagent Development. They brought the case against LifeScan. This was identification of a serious post-market safety issue. If any FDA assistance was provided to the DOJ it would have come not from ODE and pre-market but from FDA's post-market reviewers, Office of Compliance (OC) and District Office in terms of the post-market evidence of safety trends seen for the commercial devices in the trends in the submitted Medical Device Reports (MDR) [both mandatory ones from J&J and voluntary reports received from health care providers, patients and family members].(21 C.F.R.§ 803)

96. On the Department of Justice's website there is a settlement agreement between the US DOJ on behalf of the Office of the Inspector General (OIG-HHS) of the Department of Health and Human Services (HHS), the Department of Defense with LifeScan, Inc. and Johnson & Johnson; and relators Robert Konrad and John Pumphrey. On October 31, 1997 the relators Robert Konrad and John Pumphrey filed: "*USA, ex rel. Konrad, et al. v LifeScan, Inc. et al, C00-20478 JF, a qui tam action in the United States District Court for the District of Columbia*". The action was then transferred to the Northern District of California, San Jose District.

97. According to the DOJ, LifeScan entered a misdemeanor plea of guilty to information alleging, in part, it introduced and delivered into interstate commerce an adulterated and misbranded medical device in violation of 21 U.S.C. §§331(a) and 333(a)(1), in a manner captioned United States of America v LifeScan, Nic. No, CR 00-20356 JF (filed in the Norther District of California, December 15, 2000).

98. The United States contended that the Defendants submitted or caused to be submitted claims for payment to the Medicare Program (Medicare); the TRICARE program for Civilian Health and Medical Program of the Uniformed Services (CHAMPUS); the Veterans affairs Program; and Medicaid Program. Under the False Claims Act, Defendants introduced into commerce from July 1, 1996 through June 30, 1998:

> *…an adulterated and misbranded medical device, namely the SURESTEP blood glucose monitoring system, for which federal and state health care programs subsequently were caused to pay…*[24]

99. There is no specific discussion by the DOJ of the series of 510(k)s making piecemeal changes to the device that were cleared by ODE, most with a MDUFA fee paid to FDA by

[24] United States District Court for the District of Columbia Settlement Agreement, http:/www.justice.gov/sites/default/files/civil/legacy/2014/04/18/LifeScan%2C%20%20%20et20al.%20200 (last visited January 19, 2016).

Johnson & Johnson accompanying the 510(k) for the FDA's reviewer time. The DOJ discussed the success of its action based on Johnson and Johnson's billing for a commercial device that was adulterated and misbranded.

## VII. OPINION # 2:

ETHICON MARKETED PROLIFT PROCEDURE KITS IN THE UNITED STATES FOR TVM POP BEFORE ADEQUATE STUDY, DESIGN OR TESTING AND WITHOUT FDA'S 510(K) CLEARANCE. ETHICON MARKETED BOTH PROLIFT/PROLIFT+M FOR TVM POP WITHOUT A COMMITMENT TO CONDUCT ROBUST POST-MARKET SURVEILLANCE. AS A RESULT OF ETHICON'S ACTIONS, PROLIFT/PROLIFT+M WERE MARKETED TO SURGEONS THROUGH ITS OWN SALESFORCE FOR TVM POP WITH INADEQUATE INSTRUCTIONS FOR USE AND WARNINGS

**Applicable Regulations**: 21 C.F.R. § 807; 21 U.S.C. § 351(a); 21 C.F.R. § 812; 21 C.F.R. § 814; 21 U.S.C. § 352(a)(f)(1)(2)(t); 21 U.S.C. § 321(n); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 801.109; 21 C.F.R. § 820; 21 C.F.R. § 801.4 [25]

### A. ETHICON LAUNCHED GYNEMESH PS IN 2004 FOR A NEW TVM PROLIFT PFR PROCEDURE WITHOUT HAVING CONDUCTED ADEQUATE STUDIES, ENSURING PATIENT SAFEGUARDS, OBTAINING FDA'S APPROVAL OF AN IDE , CLEARANCE OF A 510(K), MONITORING OR PROVIDING AN ADEQUATE LABEL.

100. As discussed above in OPINION #1, GYNEMESH PROLENE PS was initially cleared for marketing as sheets of polypropylene surgical mesh intended for hernia and pelvic floor defects. The sheets of mesh were to be cut into shape by a surgeon and placed abdominally. It is the same PROLENE polypropylene mesh knitted from narrower diameter fiber and feels softer to the implanting physician cleared as K013718- Gynemesh PROLENE Soft Mesh on January 8, 2002. The predicate PROLENE SOFT (Polypropylene) nonabsorbable synthetic surgical mesh was cleared at K001122 in May 2000 for hernia and other defects. Prolene Soft Mesh was cleared based on Ethicon's predicates PROLENE and MERSILENE (pre-amendments mesh). Ethicon's PROLENE used in TVT for SUI was cleared based on the NDA/PMA and then 510(k) clearance history of PROLENE suture.

101. Ethicon reportedly made a "Regulatory determination" that a new 510(k) was not required before it marketed 'pre-cut sheets' of GYNEMESH PS along with insertion instruments as a PROLIFT procedure for PFR. There was no mention that Ethicon should have obtained FDA's approval of an IDE to legally conduct clinical studies in the United States for PFR.

[25] There are also a number of industry standards that support each of my opinions. For brevity, I have listed these in my reliance list.

Reportedly Ethicon was unaware the proposed new use raised significant new issues of safety and effectiveness.[26]

102. Ethicon elected not to investigate the potential effects on patients for significant changes in Gynemesh PS mesh performance properties introduced for manufacturing changes for PFR-laser pre-cutting and ETO sterilization (* significant changes for cleared 510(k) for Gynemesh PS). In October 2004, Ethicon hosted its first GYNEMESH PS Training Course that identified a cadaver was insufficient for physician training in a new blind insertion procedure because they were relying on tactile feel in the pelvis. Physicians required training with living patients to learn the anatomy and methods for insertion. Preceptors went into the OR to help guide the physician's passage of needles. It was the identification by Ethicon that the PROLIFT procedure was more complicated than initially assumed.[27] In January 27, 2005, Ethicon's "Design Verification for the Functionality of Pelvic Floor Repair Guides" (insertion tool) with sign off February 2, 2005[28] conducted per protocol BE-2004-1609. Ethicon's D 'Art Guide Needles- February 10, 2005 Design Verification for the Functionality of Sterile Cannulas (Project D-Art) sign off February 2005.[29]

103. In addition, the Ethicon sales force in "AMS FOCUS 2005," at time of launch of GYNEMESH PS was told to criticize competitor American Medical Systems (AMS) for not having conducted clinical trials and increased tissue trauma associated with insertion tools for Apogee and Perigee PFR systems. Competitor AMS marketing Apogee and Perigee (tension-free) for Minimally Invasive PFR for POP- with blind insertion. It is interesting because despite telling their sales force to do these things, Ethicon would later select these two products to be its predicates for the clearance of the PROLIFT/PROLIFT+M 510(k) (K071512).

104. In November 2005, Swiss surgeon, Dr. Jacob Eberhard, after 70 PROLIFT implants identified safety issues to Axel Arnaud, Scientific Director of Gynecare Europe. Dr. Eberhard indicated there was unacceptable risk with posterior insertion transgluteal approach near rectum, insertion guide was too sharp with risk of vascular and bowel perforation, patients aware of the implanted product, cannula and retrieval device make the implant into a rope-like shape.[30] He further comments on tools after Ethicon's February 2005 sign off of Design Validation of Guide and Design Verification of Cannulas included in Ethicon's ADD to FILE Submission 2007.[31] It is interesting because despite telling the Ethicon sales force to show the distinct differences when marketing the product, Ethicon decided to use these products as the predicate devices for the Prolift/Prolift +M 510(k).

105. As Ethicon was aware the physicians' dissection of the posterior compartment for the PROLIFT procedure was "significantly" different from standard sacro-spinus fixation

[26] ETH.MESH .00020389.
[27] ETH.MESH.002282833-34 at Exh. 15.
[28] ETH.MESH.00020400.
[29] ETH.MESH.00020409 (BE-2005-1746 Protocol [Both Included in Ethicon's August 6, 2007 ADD TO FILE Submission (ETH.MESH.00020394)].
[30] Robinson dep. 3/14/12. 350:6-373:15.
[31] ETH.MESH.00020394)- Same instruments unchanged used in PROLIFT/PROLIFT+M. 510(k)s.

procedure (Richter) or even posterior IVS. The posterior compartment dissection was identified as a technically more challenging procedure than initially thought.[32]

106. Beginning at the time of Ethicon's 2005 launch of Gynemesh PS for PFR, Ethicon limited physician training for PROLIFT Procedure only to the top 5-10% of recognized PFR implanting physicians. Even with that, there was evidence of a wide learning curve, which varied from 5 to 30 cases.[33] Despite marketing the Prolift PFR as 'Minimally Invasive' by June 30, 2006, Ethicon classified the PROLIFT PFR internally under the category of MAJOR INVASIVE SURGERIES and Ethicon's Franchise Products Requiring Major Invasive Procedures for Implantation.[34] On November 24, 2006, a team of PROLIFT experts (French study group) identified that the PROLIFT system was prone to two recurring issues: erosions and shrinkage (mesh retraction/contraction/loss of area). There was also contraction associated with recurrence, postoperative pain and dyspareunia.[35]

107. The FDA's Office of Surveillance and Biometrics (OSB) and Office of Compliance (OC), post-market arms of CDRH, as stated in ODE's pre-market August 24, 2007 FDA AI Letter identified a minimum of 174 MDRs for Gynemesh PS for an elective use in patients in its MAUDE database with patients experiencing adverse events of mesh erosion and extrusion, infection, abscess, perforations of organs, bleeding hematoma, and incontinence. The majority of patients required readmission to the hospital for additional surgery, such as removal of a portion or the entire mesh, lysis of adhesions, antibiotic therapy and blood transfusions. FDA indicated it was possible that reports were missed based on the many brand names used by Ethicon for marketing. FDA also identified 334 MDRs (including 5 deaths) for TVT. FDA requested "[P]lease provide a discussion of how the Gynecare PROLIFT System can be used safely and effectively, taking into account these reported adverse events."[36] Ethicon's response of September 2007 to FDA's Question #4 indicates that despite the major under-reporting of FDA's MAUDE database, unlike FDA, Ethicon found the reports acceptable for its new product and that additional study or testing by Ethicon was not necessary.

108. Ethicon indicated to FDA that it conducted a MDR review for Gynemesh and PROLIFT MDRs filed in FDA's database (2005-2007) and found reporting comparable. There was no reference to Ethicon having searched its own internal complaint files (post-market surveillance) and determining correlation with the number filed with FDA and trends in reporting to Ethicon. FDA did not have access to internal reports received by Ethicon globally for PROLIFT and Gynemesh. Ethicon maintained that based on its search and total sales, bench top and cadaver testing, no further clinical testing is required for Ethicon to support substantial equivalence (*i.e.* 510(k) clearance):

> *Through Design Validation and cadaver modeling, GYNECARE PROLIFT and GYNECARE PROLIFT+M have been shown not to introduce new*

[32] ETH.MESH.02282833-34,
[33] Jones dep. 1/25/2012.
[34] Exh. 16 at ETH.MESH.00329334-36.
[35] Robinson 3/14/12, P 447-451, L. 10-16, Exhibit 14; ETH.MESH.00748795, page 225 of 233.
[36] ETH.MESH.00372331.

> *issues of safety and efficacy from the predicates, GYNECARE GYNEMESH…*
> *The GYNECARE PROLIFT Instructions for Use (IFU) addresses potential adverse reactions…*
> *Placement of any surgical device, regardless of manner of placement, has the potential to result in patient injury associated with the procedure of the device.*
> *The shapes of the GYNECARE PROLIFT System was designed in response to the needs of skilled surgeons who treat pelvic organ prolapse and are familiar with the anatomy of the region.*
> *All implanted materials have associated risks, which are normally disclosed in the device labeling.*[37]

109. This information was misleading and not accurate. Ethicon's internal documents showed different risk information than it was providing to the FDA to request 510(k) clearance for marketing. Therefore, despite Ethicon's certification in the 510(k) application, the information was not Truthful and Accurate. The failure to provide the FDA with accurate risk information did not permit the FDA to follow-up and ask for additional testing to address new issues of safety and effectiveness and to consider whether or not to clear the marketing application based on the cited predicates.

### B. ETHICON FAILED TO ADEQUATELY STUDY PROLIFT/ PROLIFT+M SAFETY DESPITE PHYSICIANS', PHYSICIAN GROUPS' AND THE FRENCH REGULATORY HEALTH AGENCY'S ('HAS') CONCERNS ABOUT PATIENT SAFETY WITH 'INVESTIGATIONAL' "TVM POP KITS"

110. In November 2006, French Health Authorities (Haute Autorite de Sante-HAS) issued a report that concluded the use of mesh at the time of transvaginal repair of POP should be limited to clinical research (*i.e.* experimental).[38] Dr. Ostergard, American Urogynecology Society (AUGS) at a 2006 meeting presented his concerns about the FDA's need for better oversight of new devices. He provided examples of ProteGen (SUI Procedure Kit/withdrawn by BSC), and its implantation using Vesica bone anchors in pelvis.

111. The Transvaginal Mesh (TVM) Industry, including Ethicon, contacted key opinion leaders (KOLs) to help create a Pelvic Health Coalition ("PHC") intended to help counteract American Congress of Obstetricians and Gynecologists (ACOG's) statement that POP mesh procedure kits are '*experimental*.' The PHC then created its own "OB Gyn Management Supplement' as a publication available to members of the industry and physician proponents to refute ACOG's message to support the availability of data supporting safety and efficacy. This supplement was available to be distributed by members of TVM industry sales force to physicians to help refute physician safety concerns raised by ACOG's statement. PCH was

[37] ETH.MESH.00372341.
[38] *See* French publication and French Report- Savary D, Fatton B, Velemir L, Amblard J, Jacquetin B., What about transvaginal mesh repair of pelvic organ prolapse? Review of the literature since HAS (French Health Authorities) report, J Gynecol Obstet Biol Reprod (Paris) 2009 Feb; 38(1):11-41. Epub 2008 Nov 8.

also successful in getting ACOG to change its bulletin to remove the term "experimental" – but not the opinion about lack of data. *See* FDA's October 2008 Public Health Notification and activity of PHC. ACOG revised ACOG's Practice Bulletin #84 September 2007 to remove the word "experimental" but still continued to convey its message that patients needed adequate informed consent from physicians based on the lack of long-term safety and performance data. Despite the surmounting evidence, Ethicon did not change its messages of safety with Prolift and Prolift +M for POP nor did it revise any statements about risks associated with the device or potential device issues or retrain it sales force to update physicians about the potential risks.

### C. ETHICON ACTIVELY PROMOTED ITS PROLIFT SYSTEM FOR TVM POP–[ANTERIOR, POSTERIOR AND TOTAL]- 'OFF LABEL' WITHOUT 510(K) CLEARANCE OR AN APPROVED IDE WITH MARKETING WHICH OVERSTATED BENEFITS AND MINIMIZED RISK

112. Ethicon continued its disregard for providing physicians with adequate disclosure of risk and overstatement of benefits for Prolift and Prolift+M. An example of this is shown in its off-label promotion and misbranding by implication that Prolift had been "approved" by FDA, when in reality it had not even been cleared. In April 2006, M.D. News Edition by Tina Cauller indicated PROLIFT 'approved' by FDA in December 2004. Dr. Sarmini identified as one of first surgeons using in Texas- innovative delivery system, specialized instruments, minimize tissue trauma- developed by French surgeons in 2000 an "improved pelvic floor repair technique."

113. There were several key *misleading marketing themes for the Prolift.* Only the Prolift kit before 2008 contained prosthesis (mesh) that was not evaluated for use in the pelvis for TVM and has inserters not reviewed as part of a procedural kit. Yet, Ethicon's sales force in 2005 would tell physicians that the PROLIFT Kit alone provides devices to facilitate passage and recovery (retrieval) of prosthesis arms- to reduce the utilization of 'valves' and risk for tear on tissues" and "minimally invasive."

114. This marketing information for Prolift to physicians is inaccurate. It misstates any regulatory oversight as well as the intended use of the PROLIFT kit and instruments for a POP procedure. It is an example of misbranding and Ethicon's marketing of an adulterated device with inadequate warnings of the risks for POP, including the significant physician learning curve for performing the POP procedure.

### D. ETHICON MARKETING DROVE ITS 'LIGHTNING PROJECT' TO CREATE A 'NEXT GENERATION' PROLIFT PRODUCT TO COMBAT COMPETITORS' CLAIMS THAT 'LIGHTER WEIGHT MESH' FOR TVM POP IMPROVED PERFORMANCE

115. With reports of problems with Prolift from its KOLs, Ethicon began to look not for solutions for patient safety but for a suitable alternative mesh to use for POP. Ethicon identified among its already cleared mesh products, ULTRAPRO (K033337). UltraPro had been

cleared in April 2004, also as a general surgical mesh for repair of hernias and other fascial deficiencies. It provided Ethicon an already cleared surgical mesh candidate for selling a 'light weight mesh' to use in its Prolift PFR Kit. As a synthetic mesh it could be implanted using the same instruments as the Prolift. UltraPro was a combination of non-absorbable PROLENE and absorbable poliglecaparone (already used in cleared Monocryl absorbable sutures). UltraPro would permit Ethicon to reference (bridge) its cleared 510(k) and not have to repeat testing in any future 510(k) submitted for a modified PROLIFT+M for POP.

116. Ethicon, despite the foreseeable new potential "risks" using ULTRAPRO and poliglecaparone dosing to tissues, did not study the safety of inflammatory effects and product performance including properties of tissue healing 'in vivo' in terms of placing a large volume of UltraPro mesh and 'absorption of such a large volume of poliglecaprone' in the pelvis over time and changes to tissue ingrowth. Instead, Ethicon for the PROLIFT+M 510(k) opted to simply bridge data contained in its prior 510(k) clearances for ULTRAPRO and MONOCRYL- as part of Least Burdensome Provisions of the Food Drug Administration Modernization Act Amendment of 1997 (FDAMAA of 1997).

117. Ethicon was able to reference the prior clearance of the 510(k) for UltraPro mesh to FDA as long as it did not describe new issues of safety and effectiveness. However, that did not relieve it from having conducted its own required and adequate product design to ensure safety and efficacy of a new use for UltraPro mesh in the pelvis. That testing and study was part of required good product development practices of the medical device industry. Ethicon instead, from the internal documents, chose to disregard the good design practices of 21 C.F.R. § 820 before commercially launching Prolift+M using UltraPro mesh. Just because a manufacturer can reference a prior clearance of a mesh in a 510(k) does not mean that product will make a safe and effective surgical mesh when used for a new indication (use). The manufacturer of a mesh is still responsible for ensuring that a mesh product placed transvaginally can be placed effectively by physicians and will continue to perform acceptably before launching it to be permanently implanted in thousands of women for pelvic floor repair.

118. Ethicon also did not study the effects of manufacturing changes on UltraPro as it related to use for PFR. Such changes included mesh changes from use of laser cutting and ETO and how the changes would impact the implanted product in terms of in vivo effect for tissue. It had also not studied those in vivo effects on living tissue in the pelvis before introduction of PROLIFT (Gynecare PS mesh) for PFR kits. Considering the introduction of the new Prolift+M product, Ethicon also conducted no head to head (HTH) comparison of PROLIFT to PROLIFT+M in terms of performance even using laboratory and animal studies.

119. However, in the original June 2, 2006 510(k) comparison of PROLIFT and PROLIFT+M, the submission attempting to use Prolift as a predicate, there are significant changes in mesh mechanical properties listed in terms of strength, flexibility and rigidity between PROLIFT and PROLIFT+M, as well as change in strength over time from the effects of Monocryl absorption. These effects however were not studied by Ethicon in terms of potential outcomes (risks) for patients.

120. In addition, Ethicon's internal Material Scientists did not study the new and foreseeable risks of implanting a large volume of UltraPro (with absorbable Monocryl [cleared only for individual suture use]) to coat the female pelvis as pelvic floor repair (Total, Anterior and Posterior) and the inflammatory reaction that it could potentially trigger in the body as the body attempted to resorb (handle) the combination of absorbable Monocryl material present in Prolene mesh. The Prolift+M product like Prolift created a stimulus for tissue ingrowth. However, Prolift+M included the addition of Monocryl chemical component ( 'poliglecaprone 25[39]) created a simultaneous absorption challenge of a large amount of foreign chemical material intertwined with the Prolene mesh fibers. As FDA was not clearly informed the use of Monocryl, despite clearance for UltraPro mesh was a new risk for Prolift+M not seen for Ethicon's citation of AMS predicates Apogee (K040537) and Perigee (K040623) for transvaginal mesh PFR and POP to help it obtain clearance of K071512 in May 2008.

121. Ethicon did not attempt to simulate its proposed use of Prolift+M for PFR in terms of in vivo effects. Rather, Ethicon discounted the concerns listed in FDA's 1999 and 2002 Guidances for "Absorbable Adhesion Barriers." Ethicon, did have knowledge about the use of absorbable material testing since it had performed in vivo adhesion barrier testing. It had obtained two PMA approvals for Absorbable Adhesion Barriers, both used in the abdomen and for gynecological indications: 1) INTERCEED 1998 and 2) INTERGEL-2001 (*subsequently voluntarily withdrawn in 2003 for safety issues). However, it apparently did not perform the same testing of an absorbable material introduced into the pelvis when it failed to conduct similar types of testing for PROLIFT+M. As a 510(k) clearance for a Class II product it did not perform the known types of applicable to characterization of the in vivo effects of absorbable material in UltraPro or later in the Prolene mesh component for Prolift+M. [40]

## VIII. OPINION #3:

ETHICON'S PROLIFT/PROLIFT +M 510(K) FAILED TO ADEQUATELY DESCRIBE TO FDA THE RISKS AND DIFFICULTIES REPORTED WHEN PROLIFT WAS IMPLANTED FOR TVM POP IN WOMEN.

**Applicable Regulations**: 21 C.F.R. § 807; 21 C.F.R. § 812; 21 U.S.C. § 352(a)(f)(1)(2),(t); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 801.109.

[39] Monocryl® is a monofilament synthetic absorbable suture prepared from the copolymer of glycolide and epsilon-caprolactone

[40] *See* Guidance for Resorbable Adhesion Barrier Devices for Use in Abdominal and/or Pelvic Surgery published December 16, 1999; Guidance for Resorbable Adhesion Barrier Devices for Use in Abdominal and/or Pelvic Surgery; Guidance for Industry published June 18, 2002 at http://www.fda.gov/medicaldevices/deviceregualtionandguidance/ucm072879.htm (last visited November 12, 2015).

### A. ETHICON'S ORIGINAL 510(K) K071512 FOR "PROLIFT+M" FOR TOTAL PFR MISLEADINGLY TOLD FDA'S REVIEWER THAT PROLIFT+M TOTAL POP WAS ONLY A "*MODIFICATION OF ULTRAPRO MESH*" CLEARED FOR HERNIA REPAIR

122. UltraPro mesh was cleared by FDA to be marketed as:

> *…may be used for the repair of hernias or other abdominal fascial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result.*

123. The UltraPro IFU included the following "Actions" applicable to abdominal hernia wall repair:

> *ULTRAPRO Mesh is used for permanent stabilization of the abdominal wall, e.g. in hernia repair. The absorbable poliglecaprone part of the mesh helps keep the polypropylene structure rigid thus making intraoperative manipulation and positioning of the mesh easier. In ULTRAPRO Mesh implanted subcutaneously in rats the poliglecaparone-25-copolymer is essentially absorbed at 84 days after implantation. Due to the wide pore construction of ULTRAPRO Mesh during healing, a strong, three-dimensional collagen fiber network is formed. The residual polypropylene mesh does not hinder this process, thereby avoiding excessive connective tissue deposition and deleterious scar formation. The biomechanical properties of the polypropylene mesh, which are nearly identical to those of the abdominal wall, permit physiologically normal abdominal wall dynamics while guaranteeing optimal stability under major strain.*

124. Ethicon's 510(k) incorrectly identified PROLIFT SYSTEM Insertion Instruments as Class I 21 C.F.R. § 878.4800-"manual surgical instrument for general use" (GAD). FDA was not informed the devices were specifically adapted from Ethicon's K963329 ENDOscope Instruments (Class II devices) intended to be used with "visualization" by an endoscope.[41] The new use was without aid of "visualization" but rather with blind insertion by the physician, increasing the potential risk. Ethicon had changed the intended use and adapted the class II accessory devices its ENDOholder (cannula), ENDOLoop (Retrieval device) to be specialized instruments used in the blind insertion of its PROLIFT and PROLIFT+M System for PFR. The devices were internally validated/verified in February 2005 as acceptable for use with the PROLIFT insertion Procedure before Ethicon had received any physician feedback (from use in living patients) regarding the risks of using these instruments in patients for blind insertion for PFR. Despite the negative surgeon feedback, as FDA was not informed, the instruments were not modified by Ethicon's engineers to

[41] K963329; ETH.MESH.00020513.

address clinical feedback it had received as to proposed blind (unaided by visualization of the anatomic site) physician use for PFR in patients.[42]

125. Subsequently, the FDA was provided the following misleading information in the PROLIFT+M 510(k) despite having signed "Truthful and Accurate Statement." It is also interesting to note that Ethicon uses its own slightly modified Truthful and Accurate Statement-- not the required statement per 21 C.F.R. § 807.87(k). Ethicon's statement reads:

> ***510(k) Summary of Tech Characteristics of new device to predicate devices:*** *Like currently marketed devices, the implantable component is a sterile, mesh implant intended to repair hernia defects. The mesh implant component of the proposed device is made of nonabsorbable and absorbable polymers, which are identical to those found in ULTRAPRO Mesh, currently marketed by Ethicon, Inc.*[43]

126. This 510(k) Truthful and Accurate Statement signed by Bryan A. Lisa and Vincenza Zaddem was a modification and is non-compliant with the federal regulations. The additional processing steps for the Prolift +M include mesh relaxation and laser cutting. In addition, it found precutting is a "convenience for the end user."[44]

127. The FDA's required "Truthful and Accurate Statement" for submission of a 510(k) should consist of the information described in 21 C.F.R. § 807.87(k):

> *A statement that the submitter believes, to the best of his or her knowledge, that all data and information submitted in the premarket notification are truthful and accurate and that no material fact has been omitted.*

128. The FDA's premarket notification Truthful and Accurate Statement for a 510(k) as required by 21 C.F.R. 807.87(k):

> *I certify that, in my capacity as (the position held in the company ) of (company name), I believe to the best of my knowledge, that all data and information submitted in the premarket notification are truthful and accurate and that no material fact has been omitted.*

129. As Ethicon would be aware the FDA's filing of a 510(k) submission requires each ODE reviewer assigned a 510(k) to begin by ensuring there is a signed Truthful and Accuracy statement contained in a 510(k) submission. If the statement is not there and signed by a member of the sponsor's company (not an outside consultant) the 510(k) submission cannot be accepted for review. However, there is no requirement for the reviewer to determine that the Certification contains the exact wording above as required by the 510(k) and 21 C.F.R. 807.87(k) and has not been altered by the sponsor. The role of the FDA ODE reviewer is to

[42] ETH.MESH.00020513.
[43] ETH.MESH.00748571.
[44] ETH.MESH.00748622.

suspect that a Sponsor would provide a misleading statement and missing information from the 510(k).

130. As an example of misleading information, the Prolift+M product is not required to be submitted to the FDA reviewer. However, there is a schematic drawing. The 510(k) drawing of the PROLIFT+M mesh, as not addressed fully in the 510(k) for the reviewer, shows a significant modification in the angulation of the posterior arms for total and posterior mesh implants since the prior design of PROLIFT. There is no explanation as to the reason for the changes in structure and design. The PROLIFT design went from two arches to longer and more lateral sweeping arms (strap). [45] **However, no explanation was** provided to FDA reviewer as to the design and testing of the modification to the **posterior arms. This would be one example of a significant omission of material fact as to the clinical rationale from implantation in Prolift in patients since at least 2005 and the reason for the changes to the design proposed in Prolift+M.**

## B. ETHICON'S 510(K) DISMISSED THE RELEVANCE OF PROLIFT'S PAST HUMAN RISK INFORMATION AND ITS DIRECT APPLICABILITY TO BOTH PROLIFT+M AND WARNINGS FOR SURGEONS

131. Ethicon's 510(k) referenced Fatton and colleagues[46] experience with the use of the PROLIFT System to repair organ prolapse (POP). The study included 110 consecutive subjects at three French centers who were evaluated retrospectively. The study (published only in French) included women with recurrent prolapse and significant primary prolapse. , Ethicon's 510(k) provided the reviewer with a misleading English summary of the French study outcome stating "…[t]he authors concluded that the procedure and implants were safe, with early indication of effectiveness." [47] The FDA reviewer was not informed that these authors implanting PROLIFT (Gynemesh PS) by 2006 had identified two specific problems with the Prolift product: 1) mesh contraction (shrinkage); and 2) erosion.[48]

132. The 2006 data from the French study would be eventually published in English after 510(k) clearance in 2010. The 2010 publication discussed the risks of mesh retraction and the authors' finding that mesh retraction was worse with anterior insertion (even with total PFR) based on the authors' follow-up use of two dimensional (2D) Ultrasound imaging. In terms of Prolift and Prolift+M, Ethicon already knew based on rat data with ULTRAPRO mesh for 510(k) that its introduction into PROLIFT+M would not address the known risks of the design for recurrent POP and mesh contraction. These were the same risks seen in an Ethicon UltraPro rat study[49], and Prolift and would continue to Prolift+M.

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[45] ETH. MESH.00748621.
[46] Fatton B, Amblard J, Debodinance P, Cosson M, Jacquetin B. Transvaginal repair of genital prolapse: preliminary results of a new tension-free vaginal mesh (PROLIFT trade mark)- a case series multicenter study. Int Urogyn J. Pelvic Floor Dysfunct. 2006 Nov 28.
[47] ETH.MESH.00748571.
[48] Robinson 3/14/12, P 447-451, L. 10-16, Exhibit 14; ETH.MESH.00748795, page 225 of 233.
[49] K03337 Cleared April 1, 2004- Animal Testing- ETH.MESH.00748763-82

133. The original Ethicon 510(k) submission for Prolift+M alone also referenced Altman (2007)[50] and stated (out of context of the article): "Two additional papers described management of perioperative and postoperative management of problems associated with PROLIFT System."[51] Ethicon wrote in its 510(k) about the Collinet study: "Collinet[52] reported a manageable rate of mesh exposure problems among a series of 227 patients who underwent the system procedure for the treatment of pelvic prolapse, and identified factors that appeared to influence the probability of mesh exposure occurring." FDA, after independently obtaining and reviewing Altman, later identified that Ethicon had downplayed/not fully discussed Altman's safety concerns regarding risks of increased volume of PRF mesh when compared to SUI. FDA, found Altman to be a significant study. The FDA later referenced Altman's concerns about POP to inquire why Ethicon justified not obtaining clinical data. FDA went on to request Ethicon include reference to Altman (2007) in its IFU as one of two mandatory references for physicians. Ethicon indicated to FDA that it did not accept the request or want to comply in its responses to FDA.

134. Ethicon's citing of Collinet's findings in its 510(k) summary for FDA was not accurate. Such inaccurate representation of the medical literature is poor science as well as not permitted by the 510(k) process. Ethicon's use of Collinet[53] and Altman (2007) was not consistent with Ethicon's duty to be Truthful and Accurate with FDA in its 510(k) (21 C.F.R. § 807.87(k)). Collinet was a retrospective study of continuous patients treated with TVM POP by a vaginal approach between January 2002 and December 2003 (before marketing of PROLIFT). The authors indicated that mesh use for surgical repair of POP by a vaginal route (TVM) was not devoid of tolerability-related problems, such as vaginal erosion. There were thirty-four (34) cases of mesh exposure seen within 2-months of surgery, an incidence of 12.27%. Twenty-five (25) of the patients required partial mesh removal. As correctly indicated by Ethicon to FDA, the authors identified 'risk factors,' but Ethicon did not then provide an accurate disclosure of those risk factors to FDA or in its IFU for physicians. One primary risk factor for mesh erosion identified by Collinet (et al) was "concomitant hysterectomy" [OR=5.17 (p=10-3], a second factor was the use of an inverted T colpotomy [OR=6.06 (p=10-2)]. The authors provided two guidelines intended to help reduce mesh erosion: (1) The woman's uterus must be preserved; and (2) the number of colpotomies (incisions) needed to insert the mesh must be limited. Therefore, a women losing or without a uterus at time of TVM POP was already identified to have an increased Odds Ratio (OR) of 5.17 for developing 'mesh erosion' when compared to a woman retaining her uterus for TVM PFR for POP.[54] The increased risk of mesh erosion with loss of a uterus was not included in Ethicon's IFU or in Ethicon's discussion of risk with FDA in the 510(k).

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[50] Altman D and Falconer C. Perioperative Morbidity Using Transvaginal Mesh in Pelvic Organ Prolapse Repair. Obstetrics & Gynecology 2007; 109(2 Part i):303-308 ; ETH.MESH.00747795

[51] *Id.*

[52] Collinet P, Belot F, Debodinance P, HaDuc E, Lucot JP, Cosson M Transvaginal mesh technique for pelvic organ prolapse repair: mesh exposure management and risk factors. Int Urogynecol J Pelvic Floor Dysfunct 2006 Jun; 17(4): 315-20. Epub 2005 Oct 15.; ETH.MESH.00748795.

[53] Collinet P, Belot F, Debodinance P, HaDuc E, Lucot JP, Cosson M Transvaginal mesh technique for pelvic organ prolapse repair: mesh exposure management and risk factors. Int. Urogynecol J Pelvic Floor Dysfunct 2006 Jun; 17(4): 315-20. Epub 2005 Oct 15.; ETH.MESH.00748795.

[54] Note-Inverted "T" colpotomy refers to the type of vaginal incision used for vault prolapse surgery.

135. As the former Chief Medical Officer with ODE, a physician and a woman, I find the lack of Ethicon's accurate disclosure of known risk factors for POP associated with premature product failure, particularly when proposing implantation in women without a uterus or as part of a combination procedure with a hysterectomy by 2007 significant. This information about POP risk was important safety information for FDA, physicians and women about the use of Ethicon's product. It would also have been considered essential information for the FDA reviewer to have in a 510(k) while considering the clearance. This information would have permitted FDA to request additional information as well as provided information which Ethicon should have captured in its IFU for its commercial POP product.

136. FDA in the 510(k) submission was not provided an accurate description of the clinical information already available for PROLIFT PFR from clinical use for POP, including Dr. Eberhard's comments in November 2005 about the risks for Ethicon's insertion instruments and performance of the surgical procedure. FDA was not told that physicians were adding sutures to the anterior mesh to help keep it in place, in contrast to Ethicon's marketing as a tension free procedure. Ethicon knew that Prolift (Gynecare PS) with Prolene mesh increased risk for mesh contraction and recurrence of POP. By 2006, Ethicon knew that the Anterior PROLIFT PFR component, whether used as a stand-alone PFR or as part of a Total PFR carried greater risk for women of premature failure than Posterior PFR.

137. Ethicon, despite the reliance on experienced KOLs on 2D ultrasound, made no recommendation in its IFU to implanting physicians (or monitoring physicians) to use 2D ultrasound imaging to evaluate the status of Prolift (and/or later Prolift+M) implants in terms of early identification of mesh retraction and possible device failure. FDA and physicians were not told that Ethicon's KOLs in early October 2004 had experienced difficulties training physicians to perform the implantation technique even in cadavers. FDA and subsequently physicians were not informed of the great variability in procedure learning curve ranging from 5 to 30 cases when training for the PROLIFT procedure was restricted to only the top 5-10% of implanting surgeons prior to 2008. Internally, Ethicon classified its PROLIFT Procedure as 'Major Invasive Surgery" while its marketing described it as a minimally invasive procedure to FDA and physicians. Furthermore, the FDA (and ACOG) was not informed that the French HAS, in the country where Ethicon's research was actively pursued for PFR, issued its own report in 2006 calling TVM PFR in general for POP as 'investigational'.

138. Ethicon would later correct (update/modify) its original 510(k) submission's listing of only two centers in September as having used PROLIFT. The updated 510(k) (amendment) for PROLIFT/PROLIFT+M, after requested for clinical data to include post-market studies, described a total of three centers in the United States (starting in 2004) and eight centers in France (starting in 2005). This change in the 510(k) clinical information shows that Ethicon was aware of the inaccuracies of the information it gave to the FDA in its 510(k). That updating of clinical information was tantamount to projecting an accurate picture that it needed to change for its 510(k). It also shows that United States physicians had been implanting Prolift at three centers for POP in United States patients as an 'investigational' device without Ethicon's obtaining an FDA approved IDE and without a 510(k) clearance

since 2004. United States women were being used unknowingly for Ethicon to conduct product development (research) for it by encouraging physicians to use their own patients without a requirement for follow-up and reporting to FDA as Ethicon research subjects.

## C. DESPITE ETHICON'S MISREPRESENTATION THAT TVM PROLIFT PFR KITS FOR POP PROPOSED "*INSIGNIFICANT*" CHANGES OF GYNEMESH PS MESH, FDA REQUESTED ADDITIONAL SUPPORT FOR THE CLAIM

139. FDA did not accept as valid that Prolift was an insignificant modification of Gynemesh PS. The marketing introduction of PROLIFT mesh as a Prolift procedure kit for POP, Ethicon called a shape change (from a flat sheet) to the currently marketed Gynemesh PS mesh (Prolift) (more complex and specific), with addition of inserter tools to create a PROLIFT procedure kit. FDA was told the "preshaped mesh was made for user convenience, the inserter tools – single-patient guide, single patient cannula and single-patient use mesh retrieval device." FDA was told the inserter tools in GYNEMESH PROLIFT are identical to tools being proposed for PROLIFT +M.[55]

140. However, these changes, despite Ethicon's inaccurate statements to the FDA downplaying the changes, in 2007 were not 'insignificant' but such a rationale by Ethicon's regulatory affairs staff permitted Ethicon to profit from its quick introduction of an initial flawed POP kit to the United States market. Ethicon's corporate method it dealt with Prolift served to get a POP procedure product to physicians. It avoided having to deal with time delays and questions of the FDA's reviewer. Prolift was marketed before FDA could question the safety and efficacy of POP. Ethicon's actions appear once again to be consistent with its corporate history to disregard patient safety and FDA's role as the gatekeeper for medical devices to protect the public from undisclosed risks of new medical devices. Ethicon's actions directly go against the mandate of Congress to the FDA to conduct pre-market review to control the influx of medical devices to the market.

141. As a former Chief Medical Officer with ODE and physician, I would not classify these changes to introduce a new POP procedure kit to the market as 'not significant' and not requiring submission of at least a 510(k). Also as a former medical officer and physician would have difficulties with Ethicon's disregard of the clinical data which already showed since 2004 as the unacceptable risks of Prolift and the risk in the animal data for UltraPro mesh? Ethicon's changes for its permanently implanted synthetic mesh device as Prolift, which had already resulted in a lucrative market share for POP for Ethicon, did create significant new safety and efficacy issues for American women which Ethicon had failed to address. Ethicon compounded those risks with its 2007 510(k) submission for Prolift+M.

[55] ETH.MESH.00020389 [*No discussion in the submission of any new issues of safety and effectiveness for GYNEMESH PS kits or patient RISK for the procedure or physician learning curve].

## D. FDA DETERMINED ETHICON'S CLAIMS OF LACK OF SIGNIFICANT GYNEMESH PS CHANGES FOR TVM POP WITH PROLIFT WERE INACCURATE AND OFFICIALLY NOTIFIED ETHICON THAT ANY PROLIFT MARKETING REQUIRED A CLEARED 510(K)

142. After FDA's reviewing Ethicon's ADD to FILE submission documents, as well as the PROLIFT+M 510(k), Ethicon was informed that a mere letter to the Gynemesh Prolene PS 510(k) file to add PROLIFT was deemed by FDA as not sufficient. *See* FDA's August 24, 2007 FDA's Additional Information Letter to Ethicon.[56] The PROLIFT required a 510(k) clearance to be legally marketed by Ethicon in the United States. Ethicon could not market PROLIFT legally as a new pre-cut mesh for tension-free PFR after August 24, 2007 until May 15, 2008. Ethicon had been conducting research in women with an investigational device. Any further use of PROLIFT in the United States prior to clearance must be performed under the safeguards of an FDA approved Investigational Device Exemption (IDE) (21 C.F.R. § 812, 21 C.F.R. § 56). *See* FDA AI Letter August 24, 2007[57]. This was FDA's official notification that all violative PROLIFT PFR Kit sales must immediately be stopped in the United States as of August 24, 2007 until cleared by FDA (May 2008). FDA indicated that among the actions available, it opted to allow PROLIFT to be combined (bundled) into the PROLIFT+M 510(k) for simultaneous consideration of clearance. There was no discussion of FDA taking regulatory actions against Ethicon. There was no Dear Doctor letter sent out by Ethicon to physician (or distributors or hospital) informing them that Prolift was no longer able to be marketed and implanted in patients until it received a 510(k) clearance. Ethicon did not conduct a recall of remaining Prolift product from the field.

143. Because Ethicon did not submit information on the Prolift prior to submitting the 510(k) Prolift +M, though they were legally obligated to have done so because they made such significant changes to Gynecare Prolene PS mesh to change the intended use as kits for POP. FDA required Ethicon identifying a legally marketed TVM PFR POP predicate for obtaining 510(k) clearance of both PROLIFT and PROLIFT+M as TVM PFR Procedure kits (anterior, posterior and total). FDA also requested a predicate to clear procedure kit for blind (without the aid of visualization) physician insertion to implant Prolift/Prolift+M mesh. Ethicon submitted to K071512 "S02: Update to include PROLIFT PFR System with PROLIFT+M PFR System" on September 19, 2007[58]. FDA had specifically requested that the "Truthful and Accurate Statement" for the 510(k) be amended to include reference to both products, which Ethicon did not do.[59]

144. Ethicon's signed Truthful and Accurate Statement in K071512 S02, despite the FDA's request is that it specifically references for both products Prolift and Prolift+M and doesn't reference any product and still was modified by Ethicon. The same two statements were signed by Bryan Lisa, RA, Project Manager and Vincenza Zaddem, Senior Engineer, on

[56] ETH.MESH.00372330- ETH.MESH.00372335.
[57] ETH.MESH.00372330- ETH.MESH.00372335.
[58] ETH.MESH.00372359.
[59] ETH.MESH.00372358.

September 19, 2007. The statement was re-focused to state that "no material fact related to substantial equivalence decision has been omitted" instead of the general statement that "no material fact has been omitted":

> *I certify that, in my capacity as Regulatory Affairs Project Manager (R&D Project Leader) for ETHICON, Inc. I believe to the best of my knowledge, that all data and information submitted in this premarket notification are truthful and accurate and that no material fact related to a substantial equivalence decision has been omitted.* [60]

## IX. OPINION #4:

ETHICON'S SEPTEMBER 20, 2007 RESPONSE TO FDA DID NOT FULLY CONCUR WITH FDA'S AUGUST 24, 2007 REQUESTS FOR THE PROLIFT/PROLIFT+M 510(K) NOR DID ETHICON FULLY DISCLOSE KNOWN RISKS TO FDA.

**Applicable Regulations**: 21 C.F.R. § 807; 21 U.S.C. § 812; 21 U.S.C. § 352(a)(f)(1)(2),(t); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 801.109

### A. ETHICON INACCURATELY CHARACTERIZED PROLIFT'S SPECIALIZED TVM POP SURGICAL TOOLS AS CLASS I EXEMPT MANUAL SURGICAL INSTRUMENTS WHILE KNOWING THEY WERE BASED ON 'CLASS II ENDOCOPIC DEVICES' BUT NOW BEING USED BLINDLY BY SURGEONS WITHOUT VISUALIZATION

145. In Ethicon's September 20, 2007 response,(K071512 S02), FDA is once again incorrectly told by Ethicon that the specialized inserter tools, if sold separately, are Class I devices as described by 21 C.F.R. § 878.4800 (exempt from 510(k)).[61] The clinical performance of the instruments for PROLIFT described in the 510(k) to the FDA are not consistent with the risks described by Dr. Eberhard in 2005 after his use of the instruments in performance of seventy procedures. Also, the devices (cannula/retrieval device and guide) despite having names which sound like general manual surgical instruments do not perform functions consistent with general manual surgical instruments.

146. The instruments adapted by Ethicon to insert PROLIFT/PROLIFT+M mesh are designed to be accessories to Class II mesh, thus they also become Class II and require the same level of controls including 510(k) clearance. Ethicon has changed the intended use of its EndoInstruments, Class II devices (K963329) cleared for use with the aid of visualization using an endoscope by a surgeon. The devices have been specifically adapted by Ethicon to

[60] ETH.MESH.00372370 The FDA's premarket notification Truthful and Accurate Statement for a 510(k) as required by 21 CFR 807.87(k):
*I certify that, in my capacity as (the position held in the company ) of (company name), I believe to the best of my knowledge, that all data and information submitted in the premarket notification are truthful and accurate and that no material fact has been omitted.*

[61] ETH.MESH.00372341.

be used without visualization (based only on tactile feel- "blind insertion") for mesh placement in a woman's pelvis. Therefore, the change in intended use is significant and has essentially increased the risks for the cleared instruments and for patients. This type of change requires increased control (not reduced) and oversight by Ethicon not reduced. It is also intended to be part of a TVM POP procedure system.

147. Ethicon's 510(k) and response make no specific mention of Ethicon's K963329 21 C.F.R. § 876.1500 GCJ.[62] Ethicon in 2015 continues to market its Class II ENDOInstruments including the ENDOLoop inserted through and ENDOholder to catch suture to help with placement under visualization by endoscope surgery. These products are similar in performance and structure to Ethicon's PROLIFT blind use of Cannula and Retrieval device combination for PFR to implant mesh.

148. In April 29, 2014 FDA proposed that transvaginal mesh POP devices require PMA approval. It also proposed that Surgical Instrumentation for Urogynecologic Surgical Mesh procedure: Designation of Special Controls for Urogynecologic Surgical Mesh instrumentation.[63] The insertion instruments for TVM was officially proposed by FDA in 2014 to be made Class II requiring 510(k) clearance based on risk and availability of new information.

> *FDA is proposing to reclassify urogynecologic surgical mesh instrumentation from class I to class II. The Agency is also proposing to establish special controls for surgical instrumentation for use with urogynecologic surgical mesh. FDA is proposing this action, based on the tentative determination that general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of these devices, and there is sufficient information to establish special controls to provide such assurance. The Agency is reclassifying the surgical mesh for transvaginal repair and the urogynecologic surgical mesh instrumentation on its own initiative based on new information.*[64]

## B. ETHICON SELECTED AMS' APOGEE AND PERIGEE AS TVM POP PREDICATES WITHOUT ADEQUATELY DISCLOSING NEW RISKS RELEVANT TO TVM TO FDA AS WELL AS FOR TVM PROLIFT AND PROLIFT+M FOR POP.

149. Despite Ethicon's years of marketing focusing on the risks and problems associated with AMS PFR kits, in its September 19, 2007, (K071512 S02)[65] response to FDA's August 24, 2007[66] AI letter and need for new PFR predicates, Ethicon referenced AMS Apogee Vault Suspension (K040537) (cleared April 22, 2004) and AMS Perigee Posterior and Apical PFR

[62] ETH.MESH.00020513; ETH.MESH.00372373-ETH.MESH.00372379.
[63] 21 CFR part 884 Docket No. FDA-20140N-0297 Proposed Order Reclassification of Surgical Mesh for Transvaginal Pelvic Organ Prolapse Repair and Surgical Instrumentation for Urogynecologic Surgical Mesh Procedures: Designation of Special Controls for Urogynecologic Surgical Mesh instrumentation.
[64] *Id.*
[65] ETH.MESH.00372358.
[66] ETH.MESH.00372330- ETH.MESH.00372335.

Kits (K040623) (cleared May 17, 2004). Ethicon failed to mention to the FDA's reviewer the lack of a cleared Total PFR predicate since neither AMS Apogee nor Perigee was cleared to be legally marketed by AMS for "TOTAL" PFR. Ethicon referenced the commercial use of the two products as '*suitable*' predicates to FDA for support of the safety and effectiveness for the intended use to market its tension-free PROLIFT and PROLIFT+M for the same intended use, namely PFR. FDA was told in the Ethicon 510(k) Supplement 02 that its claims about the use of Apogee and Perigee for blind insertion were based on its review of the AMS website. FDA was not provided the years of marketing and sales information that had been used by Ethicon to market Prolift as better than either Apogee and Perigee for PFR.

150. There was no further discussion for the FDA's reviewer in the 510(k) S02 of the medical literature or the current clinical risks and marketing history associated with Apogee and Perigee PFR Kit systems that it now referenced as predicates. There was no further discussion of the history of the shared use of polypropylene mesh (PE) for both PFR and SUI procedures in the pelvis for PROLIFT, PROLIFT+M, Apogee and Perigee. Further, Ethicon referenced the two AMS cleared predicates to support that it did not think it needed to obtain clinical data to support FDA's concerns about new issues of safety and effectiveness to obtain clearance of PROLIFT or PROLIFT+M including the shared use of blind insertion by surgeons for PFR.

151. FDA was not adequately informed of the difficulties reported for Prolift with its blind insertion. Ethicon early on discovered the insertion instruments produced a steep learning curve which was not addressed by Ethicon's engineers. Ethicon knew it had trained only a specially selected upper 10% of surgeons to even learn the Prolift procedure and there were difficulties and premature failures.

152. Ethicon's amended 510(k) in September 19, 2007 (K071512 S02) indicated that PROLIFT and PROLIFT+M were both substantially equivalent (SE) to AMS' 2004 cleared Apogee and 2005 cleared Perigee PFR POP kits. Ignoring the differences between the products including differences between Prolift and Prolift+M.

153. Ethicon failed to also inform FDA that in its off-label promotion of PROLIFT began in 2005. Ethicon's sales force was instructed by sales documents, such as Ethicon's AMS FOCUS of 2005, to criticize AMS' marketing of Apogee and Perigee with having performed clinical studies showing excessive needle insertion trauma to patient tissues.

154. The Apogee Vault Suspension System specifically cited by Ethicon as a predicate for PROLIFT/PROLIFT+M was reviewed by FDA in 2004 by a non-clinician reviewer as K040537 for clearance for a new PFR indication (vaginal vault suspension) based on AMS clearance of a new mesh which AMS called 'LPP' (K033636-large polypropylene pore surgical mesh), which was the predicate to support AMS' clearance for PFR prior to clearance of Apogee for POP. As FDA was not told at any time about the Apogee clearance now being referenced by Ethicon (or AMS), LPP mesh, originally cleared by FDA for AMS in K040537, was never commercially sold for PFR since it was considered too stiff.

155. Another predicate referenced for Apogee clearance by AMS was Tyco's IVS Tunneller K010035 a device intended to position polypropylene mesh as a sling for 'SUI'. The other AMS predicates cited by AMS to clear Apogee for PFR (and Perigee) were AMS' SPARC polypropylene system slings all indicated and sold by AMS for 'SUI' (not PFR).

156. Technically, Ethicon did not inform FDA of the risks associated with Apogee and Perigee and which had been used by Ethicon's sales representatives in marketing Prolift against Apogee and Perigee since 2005.

157. As Ethicon would have known in its September 2007 response to FDA when it cited those two AMS predicate identifiers, [Apogee's K040537 and Perigee K040623], the commercial history of the only "PFR predicate" used by AMS to obtain clearance for PRF did not contribute any support of a safe and effective commercial history for use for PFR in humans since that specific mesh product (AMS LPP mesh) was never commercially sold or implanted for PFR despite AMS having clearance of K040537 in FDA's cleared 510(k) database. (21 C.F.R. § 807).[67] Apogee was essentially cleared by FDA based on prior clearances of PE mesh used only got SUI. Therefore, despite Ethicon's later statements about the differences in PE mesh between SUI and PFR, and to refute Altman (2007) concerns to FDA, clearance for SUI directly supported clearance for PFR.

158. FDA was not informed by AMS or Ethicon that AMS had begun PFR 'off-label' using SPARC PE mesh modeled after Ethicon's Prolene PE mesh for and cleared for SUI but now for a new indication of posterior vaginal vault repair (PFR). To counter AMS entrance into POP, Ethicon begun to market PROLIFT off-label using Gynecare Prolene Soft for PFR. Both PE mesh products were marketed by the sponsors to physicians off-label for transvaginal mesh for POP and both before 2007 had been associated with erosion and premature failure. FDA was not told in the 510(k)s the source of the off-label use by physicians of transvaginal mesh products for POP was coming from the TMV manufacturers like AMS and Ethicon.

159. Apogee's mesh implant shape, unlike Ethicon's PROLIFT mesh, was a pre-cut 'Y' shape with central core of reportedly LPP mesh and side-arms of SPARC PE mesh, with the implant held together by plastic rivets. The AMS 510(k) indicated that the SPARC arms were not for POP but for holding the implant secure, the PFR was by the LPP mesh. AMS' SPARC mesh was initially cleared for use only as AMS PE mesh slings for SUI. Ethicon's Prolene mesh was cleared in Ethicon's TVT procedure kits for SUI.

160. The Apogee device was considered a 'tension-free' product since, like Ethicon's PROLIFT (as well as Ethicon's TVT, TVT-O for SUI), it was intended to be held in place by tissue ingrowth into the pores of the PE mesh. The central mesh of the Apogee implant was later switched by AMS 510(k) to 'IntePro'[68] ('LPP-soft') mesh in June 3, 2005 (see K051485)(a

[67] A predicate, unless clearly specified to the FDA, is to have been an actual commercially released product so that its history can be used to support the same intended use for a patient.

[68] AMS IntePro was essentially a modified AMS' SPARC PE mesh (6 Mil fibers) cleared for SUI. LPP mesh was the same PE resin made of thinner 4 mil PE fiber and larger pores, but was considered by surgeons to be too stiff. Softening of LPP was done to make IntePro mesh feel softer to physician touch by application of a final heat

product which did actually have commercial use for PFR) and was designed by AMS to be similar to the 'soft Prolene mesh" of PROLIFT (Gynecare PS mesh). This AMS predicate with 'IntePro (LPP-Soft), despite its similarity to Prolift with Gynecare PS sold since 2004, however, it was not the 510(k) cited by Ethicon for obtaining clearance of Prolift and Prolift +M in May 2008.

161. AMS Apogee would be cleared seven months later after Ethicon's Prolift/Prolift+M in December 2008 to be marketed now with "InteProLite" mesh {*Light weight mesh (cleared December 4, 2008 K082387)- after Ethicon's PROLIFT/PROLIFT+M's May 2008 clearance.} This new AMS Apogee/Perigee clearance with InteProLite (light weight mesh) would be similar to Ethicon's marketing claims to physicians for 'Prolift+M'(partially absorbable PE mesh with loss of Monocryl from Prolene) . The marketing for both Prolift+M and AMS Apogee (and Perigee) with InteProLite to physicians was for unproven benefits associated with implanting a 'light weight mesh'. This benefit was based on the surgical hernia medical literature not from data from the pelvis.

162. Ethicon, unlike AMS which sold an InteProLite mesh, claimed to have a lightweight mesh for PFR only after the absorption of Monocryl out of the PE mesh. AMS claimed a lightweight mesh based on manufacturing changes (* a change in PE fiber size to 3mil from 4mil) which made the AMS mesh appear to be lighter weight to surgeons. AMS, unlike Ethicon in 2008, would also come out with a new and modified PFR system called 'Elevate PFR System' which combined InteProLite mesh, totally eliminated the SPARC supporting arms (6mil fibers), continued its use of plastic rivets to hold the PRF mesh together, but dropped tension free and added plastic anchor (harpoon)-shaped fixation elements to hold the mesh anchored into the patients' pelvic mU.S.C.les.

163. However, as FDA was not adequately informed by Ethicon in its September 2007 response for the PROLIFT+M 510(k), AMS had unofficially ("off-label") launched Apogee and Perigee in the United States using its new 'IntePro Lite' mesh before obtaining 510(k) clearance in 2008 beginning in August 2007.[69] Ethicon's changes made to PROLIFT and PROLIFT+M were made to track changes of its competitors, not based on ensuring 'patient safety.' Ethicon was requesting FDA's clearance to make changes to its marketed implanted mesh from soft (Gynecare PS) (Prolift sold off-label since 2004) to its light weight (UltraPro) Prolift+M all without having conducted adequate study or obtaining clinical data or having a commitment to long-term follow-up but to address physician perceptions about mesh. The benefit of 510(k) clearance for Prolift+M for Ethicon would allow it to more aggressively imply to physicians that FDA had somehow accepted (approved/validated) the new Prolift+M product for PFR did produce a 'lighter weight mesh' when the Monocryl component was absorbed.

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process. The next generation InteProLite was an extra light mesh, also designed to address physician perception, not science, made of AMS's same PE resin but with 3mil fibers. Each of these changes to the feel properties of the PE mesh by AMS brought about new potential and unaddressed risks. The same was true for the changes introduced by Ethicon to address physician preference for marketing, not valid science of improved performance in a patient. Physician preference for TVM mesh was largely driven by the surgical hernia medical literature.

[69] Business Services industry American Medical Systems Launches MiniArc at American Urogynecologic Society's 28th Annual Scientific Meeting. Business Wire, Sept 26, 2007.

164. There were major differences between the AMS systems and the proposed Ethicon products not addressed by Ethicon in its September 2007 (S02) submission. The Apogee Vault Suspension System consisted of the use of specialized needles and connectors which all had been called 'class I' by AMS and not cleared by 510(k). These tools were adapted specifically to pass AMS polypropylene mesh slings blindly into the woman's pelvis to provide mechanical support for the vaginal vault. Neither AMS nor Ethicon, despite marketing claims, had ever been cleared for bladder or rectal organ repair, despite both conducting off-label marketing for uncleared/unapproved cystocele and rectocele repair.

165. The cleared indications for use for the Apogee Vaginal Vault Suspension System for PFR with LPP mesh (K040537) the predicate cited by Ethicon September 19, 2007:

> *The Apogee Vault Suspension System is intended for use in vault suspension to treat pelvic organ prolapse.*

166. AMS' Perigee System was cleared as **K040623** on May 17, 2004. It was cleared also with LPP predicate (a mesh never commercially sold for PFR since considered too stiff) and SPARC mesh slings used for SUI. Perigee unlike Apogee for vaginal vault suspension was intended for placement of graft material in the '*anterior vaginal wall*' via the obturator foramen. K040623 shared the same mesh history as Apogee beginning with LPP, (IntePro and later InteProLite). However, unlike Apogee, it had a specified 'obturator foramen route' for insertion. The transobturator (TO) insertion technique was also used for Ethicon's TVT-O (obturator) (SUI) and AMS' Monarc (SUI) products with mesh and instruments intended for inserting a polypropylene mesh sling for SUI. Perigee's Intended Use Statement for Anterior PFR included reference to the TO approach used for SUI:

> *The Perigee System is intended for the placement of graft material in the anterior vaginal wall via the obturator foramen for the treatment of anterior vaginal wall prolapse.*

167. At the time of Ethicon's PROLIFT+M 510(k) application's review in 2007 and by the time of clearance on May 15, 2008, AMS already had in-house at the FDA under review by another FDA reviewer its 'next generation' PFR System Kit. AMS' next product was "Elevate System with IntePro Lite for POP PFR". (*See* K080185). This was no longer a tension free PFR kit like Apogee (PROLIFT/PROLIFT+M) or Perigee but an anchored PFR mesh kit using permanent placement in the pelvis with soft tissue anchors to hold the mesh to aid with tissue ingrowth. Elevate was cleared by FDA on April 10, 2008, only one month before Ethicon's PROLIFT/PROLIFT+M clearance in May 2008.

168. As with other AMS and Ethicon products for TVM, Elevate PFR Kits had actually already been commercially launched 'off-label' by AMS before its 2008 clearance by the FDA, so Elevate was a PFR procedure kit already introduced to key surgeons as well as to members of Ethicon. The predicate cited by AMS to market its next generation Elevate System was AMS 'K051485- AMS Pelvic Floor Repair System'. Elevate was cleared as a modification of the AMS Apogee System, and as with PROLIFT and PROLIFT+M, no clinical data was required of AMS to obtain clearance from FDA.

169. AMS' K051485 was a 510(k) clearing AMS Pelvic Floor Repair System Kits broadly. AMS cleared its current line of PFR products (Apogee and Perigee) on August 3, 2005 for broader general surgical mesh indications (urological, gynecological and gastroenterological) including both PFR and SUI. Predicates referenced included the AMS SPARC, MONARC slings for SUI, LPP mesh (never marketed) and MAS' now cleared IntePro (LPP-soft) mesh. Unlike the two predicates selected to be cited by Ethicon in 2007, (K040537; K040623) these products with AMS SPARC and IntePro mesh shared commercial histories for both PFR and SUI. However, Ethicon in 2007 did not elect to reference the additional AMS 510(k) as a predicate for PROLIFT (Gynemesh PS and PROLIFT+M) for PFR:

> *The AMS Pelvic Floor Repair System is intended for use where the connective tissue has ruptured or for implantation to reinforce soft tissues where weaknesses exists in the urological, gynecological and gastroenterological anatomy. This includes but is not limited to the following procedures: pubourethral support, including urethral slings for the treatment of incontinence, vaginal wall prolapse repairs including anterior and posterior wall repairs, vaginal suspension, reconstruction of the pelvic floor and tissue repair. (K051485 AMS PFR Repair System Kits)*

170. The above discussion was provided to show the marketing competition between only AMS and Ethicon for market share for PFR in 2007-2008 and the widespread history of off-label marketing without actions taken by the FDA. The examples also show the adept selection of predicates in 510(k)s. Both of these companies had corporate histories that accepted violating the law in order to rush to market new SUI and PFR product to obtain physician implanters without first conducting adequate science or encountering FDA delays with clearance. The FDA in 2004-2008 was not viewed as a significant obstacle to either AMS or Ethicon to start selling new TVM products to physicians. The above was also provided as another example of Ethicon's willingness to fail to adequately disclose materials facts to FDA's reviewers about its new medical devices as well as the risks of the predicate devices referenced in its 510(k) in an apparent disregard or lack of understanding of its role to ensure its own compliance with the Act. FDA was not informed that Ethicon was aware of known risks for erosion and premature failure for Prolift and Prolift+M and the AMS predicates.

171. Another similar example of known information for Ethicon not adequately described to the FDA is its use of the original predicate for obtaining clearance as a pubourethral sling called Tension Free Vaginal Tape (TVT) on January 28, 1998. Ethicon referenced the only predicate as Boston Scientific Corporations (BSC) cleared ProteGen mesh[70]( cleared on

[70] ProteGen Mesh was a surgical mesh fabric made by Meadox Products acquired by BSC in 1996 which was adapted from PMA approved and 510(K) cleared Hemashield, a collagen impregnated synthetic polyester fabric. BSC was able to simply bridge the information already contained in the PMA and 510(k)s for Hemashield as support of safety and efficacy for implantation to obtain 510(k) clearance for use for a pubourethral sling without having to supply FDA with clinical testing. The collagen had been applied to the polyester fabric for Hemashield used for vascular grafts to prevent blood leakage. There was no history of use in the pelvis as a pubourethral sling.

November 15, 1996) for use as a surgical mesh with an indication as a pubourethral sling (K963226). Of interest is that Ethicon did not cite ProteGen, now off the market by the silent withdrawal actions of BSC, as a predicate for vaginal wall repair and PFR in K071512 in September 2007 since ProteGen had been cleared for both those indications in 1996. The cleared indications for the bovine-collagen impregnated surgical polyester mesh sold by BSC as ProteGen for a pubourethral sling:

> *The proposed Surgical Fabrics are implants which are intended to reinforce soft tissue where weakness exists as urological, gynecological and gastroenterological anatomy inclusive but not limited to the following procedures: pubourethral support, urethral and vaginal prolapse repair, colon and rectal prolapse repair, reconstruction of the pelvic floor, bladder support, and sacrocolposuspension.*

172. The sponsor of ProteGen BSC acquired the Vesica Bone Anchor 510(k) as a method for the surgeon anchoring a ProteGen mesh sling in a woman's pelvic bones to treat her symptoms of SUI. The ProteGen product was launched in 1997 as a commercial minimally invasive ProteGen Sling kit with insertion tools and bone anchors. By June 1997, only four months after product launch, BSC started to receive reports of serious complications occurring with ProteGen and patient need for revision surgery. Physicians (and industry) quickly became aware that the product began to fail with reports of erosion and dehiscence and need for additional surgery for sling removal. By March 1998, BSC had made an internal decision to replace the commercial product but would continue to market the current flawed product until a new alternative product could be developed. On January 1999, BSC stopped all ProteGen sales, a total of 23 months after the National Sales Launch of February 1997. BSC conducted a voluntary Class II recall beginning January 22, 1999 ( completed by April 6, 1999) removing ProteGen product from distribution.

173. Ethicon at no time in referenced ProteGen as a predicate for initial clearance of K974098 as a pubourethral sling (TVT) indicated to FDA the difficulties being reported with ProteGen for treatment of SUI as a pubourethral sling. The cleared indication for TVT:

> *The TVT device is intended to be used as a pubourethral sling for treatment of stress urinary incontinence (SUI), for female urinary incontinence resulting from urethral hypermobility and/or intrinsic sphincter deficiency.*

174. TVT was unique for a TVM in that it was cleared based on Ethicon's submission of clinical data in lieu of collecting animal data originally requested by the FDA regarding the physician's ability to use the components of the pubourethral procedure kit to implant a tape sling. Ethicon wrote about its support for SE in Technological Characteristics and Performance Data to ProteGen:

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However, as with Ethicon's Prolift and Prolift+M with the ability to simply bridge information in already cleared 510(k)s, BSC was not relived from the burden of design and testing to ensure that its ProteGen was a safe and effective product. Commercial use of implanted ProteGen quickly showed physicians the product failed prematurely when implanted in women for treatment of SUI.

> *Technologically both the new device and predicate device are the same (i.e. both are meshes that provide pubourethral support). Additionally, both devices utilize accessories for use in the surgical procedure. Any differences between the two devices do not raise new questions of safety and effectiveness.*
> *Results of clinical evaluations were used to show that the TVT System functioned as clinically intended. Sufficient data has been gathered from clinical testing to assess that the TVT System performs as clinically intended. (K974098)*

175. Ethicon's next clearance by FDA for a TVT product was for its TVT (K012628) was cleared October 26, 2001.The predicate was Ethicon's Gynecare Tension Free Vaginal Tape (TVT) cleared by K974098. Ethicon had it cleared for the same intended use, there was no discussion of a change in insertion route to transobturator or that there was any new claims of improved safety with a transobturator insertion. The device was modified to a TVT Blue device and included the description of the accessories for insertion. There was no clinical data provided but the 510(k) stated " bench testing and preclinical evaluation to support SE of the two products". K033568 was Ethicon's clearance of a Gynecare TVT-Obturator (TVT-O) System on December 8, 2003. Performance data now indicated "results of verification testing indicates that the product meets established performance requirements."

176. Indications for use when cleared in 2003 TVT-O:

> *GYNECARE TVT Obturator is indicated for treatment of stress urinary incontinence (SUI), for female urinary incontinence resulting from urethral hypermobility and/or intrinsic sphincter deficiency.(K033568)*

177. Indications for use –September 28, 2012 TVT-O is now as a 'sub-urethral sling':

> *The GYNECARE TVT Obturator device is intended for use in women as a sub-urethral sling for treatment of stress urinary incontinence (SUI) resulting from urethral hypermobility and/or intrinsic sphincter deficiency.(FDA letter September 28, 2012, K033568)*

178. Dr. Ostergard, a founding member of the American Urogynecology Society (AUGS) at the 2006 AUGS meeting presented his concerns about FDA's inadequate oversight of new medical devices for urology. He provided as his examples recent implants/devices which had led to disappointing outcomes. He included in his discussion the ProteGen sling with sling suspension by Vesica bone anchors (K971139). This was information about an unsuccessful SUI product available to Ethicon to consider before it proceeded with obtaining FDA's clearance of Prolift+M, particularly when it knew the Prolift clinical data since 2004.

179. In follow-up to this discussion in terms of the continued clearance of 510(k) devices, the BSC 510(k) (K963226) used to launch marketing of its ProteGen pubourethral sling, despite

having been voluntarily removed from the market by BSC as a sling sold for SUI in January 1999, continues to remain an active 510(k) on FDA's website. It can be used by any medical device sponsor to support obtaining clearance of a synthetic mesh 510(k) as a predicate in 2015.

### C. ETHICON'S 510(K) DID NOT DISCLOSE TO FDA A 2005 PUBLISHED REVIEW OF TVM PERIGEE & PROLIFT FOR TVM POP AND THE AUTHORS' CONCERNS ABOUT THE NEED FOR LONG-TERM SAFETY DATA

180. Walters and Paraiso (2005)[71] of Cleveland Clinical published a review of transobturator (TO) tension-free vaginal mesh techniques for anterior vaginal wall prolapse looking at two mesh POP PFR procedure kits: AMS Perigee and ETHICON's Anterior PROLIFT and the need for cystoscopy post-insertion to ensure the bladder and ureters have not been injured. As FDA was not told in Ethicon's 510(k) or in its September 2007 (S02) response, the placement of mesh into the anterior wall for POP repair was still considered controversial by TVM implanting physicians. The authors were indicating that comparative studies of mesh PFR to traditional sutured repairs had not been performed and vaginal mesh erosion continued to remain a new problem for these procedures with a "significant number" of patients requiring reoperation for mesh removal. The authors' final conclusion was that: "These techniques await safety and efficacy studies but are increasing in use."[72] In its August 24, 2007[73] AI letter, FDA questioned Ethicon about the complexity of the proposed PROLIFT PROLIFT+M procedures and the "blind" manner the mesh was inserted with specialized tools. Ethicon's Response #5 September 2007 was:

> *The shape of the GYNECARE PROLIFT System was designed in response to the needs of skilled surgeons who treat pelvic organ prolapse and are familiar with the anatomy of the region. In addition, the shape of the GYNECARE PROLIFT and PROLIFT+M Systems are similar to currently marketed AMS Apogee and AMS Perigee Systems as per the diagrams/photos below…*[74]

181. Subsequently, FDA is then provided only the diagrams and shapes of PROLIFT and PROLIFT+M not the shapes of Apogee or Perigee mesh for comparison to referenced predicates. There is no explanation provided to the FDA for the modification in the posterior aspect of the mesh shapes for PROLIFT and PROLIFT+M shapes. There is no mention that AMS does not market a Total PFR kit. The FDA is provided only a picture of AMS Perigee System inserter tools (K040623) curved needles for anterior mesh ONLY insertion. There is no side-by-side comparison of the inserter tools used by AMS and

[71] Walters MD, Paraiso MF. Anterior vaginal wall prolapse: Innovative surgical approaches. *Cleveland Clinic Journal of Medicine* 2005 Dec; Vol 72 (Suppl 4): S20-S27.
[72] *Id.*
[73] ETH.MESH.00372330- ETH.MESH.00372335.
[74] ETH.MESH.00372341.

PROLIFT/PROLIFT+M and no explanation of the differences in terms of blind insertion and patient safety and efficacy.

### D. ETHICON'S SEPTEMBER 20, 2007 RESPONSE #5 FAILED TO ADEQUATELY DISCLOSE THE KNOWN RISKS AND DIFFICULTIES, INCLUDING THE PHYSICIAN LEARNING CURVE, ASSOCIATED WITH TVM PROLIFT INSERTION FOR POP

182. Ethicon continued in its response to FDA's non-clinical reviewer, Dr. Dang, that PROLIFT was "substantially equivalent" to **GYNEMESH**.[75] This is consistent with PROLIFT being called by Ethicon an insignificant change for Gynemesh Prolene PS:

> *Although the Design validation report exhibits a mesh placement that may appear complex, the knowledge and dissection of these spaces are [a] part of a gynecologists' training. Therefore the anatomical region is not considered "complex" to a trained gynecologist. For the Gynecare PROLIFT System, cadaver modeling and Design Validation presented no issues of safety and efficacy in relation to user interface with the device.*[76]
> *ETHICON believes that the results of pre-clinical, benchtop testing, cadaver evaluations, provide evidence of substantial equivalence of the PROLIFT Systems to the currently marketed GYNEMESH and demonstrate that surgeons can use the device without problems.*[77]

183. This response is inaccurate, misleading, and significantly downplays the known risks and fails to provide FDA with an adequate response as to Ethicon's knowledge by September 2007 about difficulties with its PROLIFT procedure insertion, difficulties with physicians training in the PROLIFT procedure, Ethicon's arbitrary restriction of implantation training in PROLIFT procedure to the top 5-10% of implanting surgeons for PROLIFT/PROLIFT+M, problems and safety concerns reported to Ethicon directly from an experienced surgeon with Ethicon's Design Validated" insertion tools, as well as the known risks for mesh contraction, recurrent POP and erosion.

184. Ethicon in its September 2007 response to FDA failed to adequately disclose information applicable to its providing an adequate label, patient brochure, physician training materials, marketing claims, and its knowledge of a need for long-term follow-up. Ethicon was aware of new issues of safety and effectiveness for both PROLIFT and PROLIFT+M in September 2007. These issues were not being addressed by Ethicon before the commercial release of its latest PFR kit in wide market distribution in the United States for permanent implantation in patients. A responsible action by Ethicon would have included its voluntary conducting

[75] Ethicon's PROLENE mesh used for slings (TVT) for SUI and sheets of mesh for surgical hernia repair, not the Apogee or Perigee predicates for PFR.
[76] ETH.MESH.00372346.
[77] ETH.MESH.00372347.

of clinical trials with PROLIFT+M and an internal commitment to obtain post-market data, including establishing a registry.

185. Ethicon's response to the FDA on September 2007 provides evidence of an important regulatory omission of 'material fact' from the 510(k). Ethicon's actions did not permit FDA to follow-up and ask for additional information (AI) as to how Ethicon planned to take steps to effectively and specifically address the PFR product risks it had already learned about from its years of off-label clinical use of PROLIFT, and applicability to actions with PROLIFT+M. This response by Ethicon was not consistent with its Certification of Truthful and Accurate Disclosure for PROLIFT and PROLIFT+M.[78]

## X. OPINION # 5:

ETHICON MODIFIED THE MANDATORY 21 C.F.R. 807.87(k) ) TRUTHFUL AND ACCURACY STATEMENT'S WORDING IN ITS 510(k) WITHOUT ANY DISCLOSURE OF THE CHANGES TO FDA'S REVIEWER.

**Applicable Regulations**: 21 C.F.R. § 807.87(k); 21 U.S.C. § 352(t); 21 U.S.C. § 331(a)(b); 18 U.S.C. § 1001

186. FDA's 21 C.F.R. § 807.87(k) requires each Premarket Notification contain a mandatory signed Truthful and Accurate Statement for both a 510(k) and a PMA. The Statement must be signed by a responsible person from the firm (*e.g.* not an outside consultant or third party). The known process at the FDA for filing pre-market submission for FDA to merely look at a submission using a checklist to ensure a signed Truthful and Accurate Statement is present in the submission. If not present, the submission is not accepted for filing. Since the wording is mandatory, the process does not require the FDA reviewer to examine the wording of each signed statement. The same process occurred with Ethicon's Gynemesh PROLENE PS 510(k) cleared in 2002 as well as ULTRAPRO Mesh 510(k) cleared in 2004. The object of the statement, required since the 1990s, is to attest to FDA that "no material fact has been omitted" from the submission. *See* 21 C.F.R. § 807.87(k).

187. The material facts relevant to FDA as it considered clearance of a PROLIFT and PROLIFT+M 510(k) would have been disclosure to FDA of 'material facts' not just material facts relevant to SE determination. For example, material facts for FDA for PROLIFT and PROLIFT+M would have included performance of AMS predicates, the performance of PROLIFT outside the United States, issues reported for PROLIFT and PERIGEE in the medical literature, the French Regulatory Agency (HAS) review released in November 2006 calling the mesh PFR POP products investigational. Also material to FDA would be the safety concerns of PROLIFT risks by Dr. Eberhard after performing 70 PROLIFT implant procedures when attempting to use Ethicon's proposed PROLIFT insertion tools.

[78] *See* OPINION #1, *infra*, regarding information already discussed about risk not adequately provided or discussed with FDA for the PROLIFT PFR procedure in September 2007.

188. Also, I would find as a former Chief Medical Officer in ODE that material necessary to the review of a 510(k) would be that Ethicon's PROLIFT experts in France in 2006 identified risks for erosion and even more significant risk of mesh contraction, describing a method for recurrence of POP with PROLIFT, mesh contraction greater on the anterior aspect when compared to posterior and that Ethicon knew that ULTRAPRO also contracted, so the risk of mesh contraction was not be solved by Ethicon's changing to UltraPro.

189. Material facts for FDA for a 510(k) would include an adequate description by Ethicon of the complexity and difficulty encountered by physicians as early as 2004 in the 510(k) as well as in the surgical techniques manual and physician training. It would have been material for a 510(k) reviewer that use of cadavers alone could not be used to train physicians adequately to be able to implanting PROLIFT without visualization (blindly) in a living and breathing patient. Also material for the 510(k), product labeling and FDA was that Ethicon had artificially limited training in PROLIFT insertion technique through 2008 only to the top 5 to 10% of PFR physicians and even still there was a significant and wide learning curve. A material fact to FDA was that Ethicon had no idea how the 2nd tier physicians would do when attempting to learn the PROLIFT/PROLIFT+M procedure with wide commercial release. A material fact to the 510(k) and the FDA's review was that Ethicon internally listed PROLIFT and PROLIFT+M as 'MAJOR INVASIVE SURGERY.' Material facts not accurately disclosed to FDA was Ethicon's marketing of PROLIFT beginning in 2005 with criticism of AMS for launching Apogee prematurely without conducting clinical studies.

190. Another material fact that should have been disclosed for FDA's non-medical reviewer in Surgical Devices, and as a former Chief Medical Officer in ODE and current regulatory consultant within the FDA who has worked with providing clinical support for ODE's reviewers, I believe would have been important for Ethicon to disclose in its 510(k) to the surgical device reviewer was Ethicon's prior history and experience with the Ob/Gyn Devices branch with absorbable barriers for women including INTERCEED approved as P880047 approved in 1989. Also important was the withdrawal of INTERGEL (P990015, approved November 2001), an absorbable adhesion barrier product sold to gynecologists for a short time for use in the abdomen and pelvis of women, but subsequently withdrawn from the world market by Ethicon on April 16, 2003 based reportedly on 'user error'.

191. Ethicon was promoting the safety of PROLIFT+M to expand the use of UltraPro mesh beyond the cleared hernia repair indication for surgery and the use of its cleared absorbable poliglecaparone-25 (K964072; K960653; and K930772) to include a new expanded use beyond surgery in a new area of anatomy, the female pelvis for PFR. As not apparently addressed by Ethicon's scientists for the FDA reviewer or in the design of the product, as proposed for PROLIFT+M the body would need to be able to absorb a much larger amount of poliglecaparone-25 over the larger surface area of the female pelvis while embedded within a PE mesh. The body would be have to simultaneously cope with reabsorption of the poliglecaprone 25 load and tissue ingrowth in the PE mesh pores as well as the stability of a foreign body placed within the motion of the female pelvis. This was far beyond the 510(k) clearance and demands of a body to incorporate a sheet of UltraPro mesh surgically anchored in the abdominal wall for hernia repair.

192. Ethicon had obtained PMA approval of an absorbable solution product called INTERGEL(a 0.05% ferric(iron)- hyaluronic acid (Fe-HA) gel (P990015) in November 2001 for Ob/Gynecological surgery as an adjunct to good surgical technique intended to help reduce adhesions. After a gynecological procedure, the surgeon was to infuse the solution into the abdomen or pelvis to help reduce adhesions. INTERGEL's PMA approval was based on Ethicon's claims, studies with open gynecological surgery, and assurances of safety and efficacy. However, FDA initially denied approval based on a lack of sufficient support for PMA approval. Ethicon disagreed with the FDA's ODE reviewers and management determination. Johnson and Johnson's went to a formal dispute resolution hearing actions with INTERGEL to dispute FDA's denial as not founded. The Johnson and Johnson action against the FDA was headed by external regulatory consultant Karen Becker, Ph.D. Johnson and Johnson prevailed convincing the non-FDA experts on the Panel, which recommended that FDA approve the PMA. As a result of Ethicon's efforts, the INTERGEL PMA was subsequently approved (November 2001). However, within less than two years later on April 16, 2003, based on unacceptable risk for patients and serious adverse events, Ethicon voluntarily withdrew INTERGEL from the global market "urging customers to immediately stop using this device."[79] The official statement provided by the FDA about the Gynecare Urgent Withdrawal was that Gynecare considered the issue a user (surgeon) issue based on 'off label' sue of surgeons with laparoscopy, and not a fundamental issue with its design and testing as an absorbable gynecologic product. No mention by FDA that it was made aware that Gynecare sales reps had been promoting Intergel off label to gynecologist for use following laparoscopy. Since most gynecological surgery is now performed with laparoscopy to reduce adhesion formation and a hysterectomy is one of the most common gynecological procedures, the risks discussed in FDA's statement should have been foreseeable to Ethicon and addressed within its own marketing and product testing. FDA wrote about the Intergel withdrawal based on the information it had received from Gynecare about the action. The launch of Intergel in the United States was only after November 2001:

> *The product is intended to be used in open, conservative gynecological surgery as an adjunct to good surgical technique to reduce post-surgical adhesions. GYNECARE is conducting this voluntary withdrawal to complete an assessment of information obtained during post-marketing experience with the device, including adverse events associated with off-label use in laparoscopy and non-conservative surgical procedures such as hysterectomy.*
> *Post-market reports include late-onset post-operative pain and repeat surgeries following the onset of pain, non-infectious foreign body reactions, and tissue adherence. In some patients a residual material was observed during the repeat surgery….*
> *GYNECARE is withdrawing the device from the market to conduct a full and thorough assessment of technical issues, surgical techniques and*

[79] ETH.MESH.002282833- ETH.MESH.002282834; FDA Statement: Urgent Global Market Withdrawal: GYNECARE INTERGEL Adhesion Prevention Solution Voluntarily Withdrawn from the Market by GYNECARE Worldwide April 16, 2003.(http://www.fda.gov/safety/medwatch/safetyinforamtion/safetyalerts for human medical products)

> *circumstances associated with post-market events. From the launch of this device in 1998 to February 2003, the overall complaint rate worldwide is low.*[80]

193. There is an FDA's 2005 Science Forum Abstract, P-16 presented by a group of FDA scientist's at the FDA on at an internal Science Forum event. MD Luu, et. al. subsequently presented the group's findings of its CDRH research study looking at Intergel (Fe-HA gel) as a source of certain reported adverse events. The abstract's background was that approximately 5 million general and Ob/Gyn surgeries occur each year in the United States, with 50-95% patients developing post-operative abdominal and pelvic adhesions. "*We present a case of post-market incident involving Intergel,…used as preventive abdominal pelvic adhesion barrier in women.*"[81] In terms of Intergel's production: *" Preliminary experiments suggest that Intergel formulation procedure produces non-homogeneous Fe-HA gels due to poor control of cross linking uniformity.*" Therefore, the FDA's scientists in 2005, two years after the product was withdrawn for the market, were not indicating the same 'user error' as stated in the FDA's 2003 statement based on information from GYNECARE. Instead a group of CDRH scientists looking at the post-market issue indicated the problem with the Fe-HA appeared to be the result of poor manufacturing and quality control, definitely a production problem. "*FTIR spectra of an explanted patient tissue sample suggest post op residual Intergel.*" The conclusion of the FDA' scientist group looking at Gynecare's Intergel from only a small 'post-marketing' aspect of an absorbable product:

> *We believe that the lack of manufacturing control process for the percent cross linking of Fe-HA could lead to non uniform visco-elastic properties, and compromise the ability to spread and degrade in vivo. This could explain for the adverse events which include post-op pain, non infectious peritonitis and foreign body reactions.*[82]

194. Intergel, despite not being marketed, still has PMA P990015 as approved and on the FDA's website for approved PMAs. The last approval for the PMA was supplement S002 approved on March 18, 2003 to update the label with post-market risk information. The PMA had been reviewed and approved by reviewers in FDA's ODE Obstetrics and Gynecology Devices Branch. Neither this PMA, nor the Interceed PMA- with last PMA supplement approval July 2015, was handled by ODE's General Surgical Devices Branch were the PROLIFT+M and TVM products were reviewed and cleared by 510(k) for POP. Therefore, as Ethicon would be aware, it was unlikely that the General Surgery Devices Branch reviewers were adequately informed or even involved with its approval of absorbable products for Ob/Gyn surgery. It would also be unlikely that this review branch had been involved in the development of FDA's Guidance for Industry titled "Resorbable Adhesion

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[80] FDA Statement: Urgent Global Market Withdrawal: GYNECARE INTERGEL Adhesion Prevention Solution Voluntarily Withdrawn from the Market by GYNECARE Worldwide April 16, 2003.(http://www.fda.gov/safety/medwatch/safetyinforamtion/safetyalerts for human medical products/)

[81] 2005 FDA Science Forum P-16 Luu, MD, Isayeva IS, Vorvolakos K, Patwardhan DV, Das S. Materials Issues in the Post-market Experience of the Ferric Hyaluronic Adhesion Prevention Solution (Fe-HA) (http://www.accessdata.fda.gov/ScienceForums/forum05/P-16.htm.

[82] *Id.*

Barrier Devices For Use in Abdominal and/or Pelvic Surgery"83 issued June 18, 2002 or thee earlier guidance with the same title published on December 16, 1999. This applicable guidance is not referenced in Ethicon's Prolift+M 510(k) as a guidance utilized by Ethicon to test and develop and obtain marketing clearance for either UltraPro mesh or Prolift +M. The Guidance also requires obtaining clinical data via an IDE for eventual PMA approval. The poliglecaprone 25 of the Prolift+M is not intended as an adhesion barrier, however, it shares the properties of an absorbable material. Information in the guidance regarding the use of absorbable materials particularly dosing and pharmacokinetics should have been considered by Ethicon as it considered the new use of a large amount of absorbable material in the pelvis. FDA's guidance had for the sponsor to consider in terms of the dose of the material given to a patient (i.e. dose of poliglecaprone 25 in a pelvic floor repair-total, anterior, and posterior):

> *In all biocompatibility and toxicity testing, the dose of the product used should reflect a reasonable safety margin compared to the doses proposed for sue in humans. Generally, you should test a range of doses, up to ten times the highest dose to be used in humans, or provide a justification for a smaller safety margin…*[84]
>
> ***Testing for Delay or Prevention of Healing****- Inflammation and the replacement of soft tissue with fibrous tissue is an expected outcome of the normal healing process. Reducing the formation of adhesions may also delay or prevent healing. This should be tested in animal studies….*
>
> ***B.Pharmacokinetic Studies***
>
> *You should conduct pharmacokinetic studies to determine the absorption, distribution, metabolism and excretion (ADME) route(s), mechanism(s) and timeline of excretion of the product.*
>
> **C. Effectiveness Studies**
>
> *You should conduct effectiveness studies in appropriate animal model(s) to provide "proof of concept". That is, these studies should suggest that there is a reasonable premise for efficacy in the human. Animal studies may also suggest better designs for the clinical studies to follow.* [85]

195. By 2007 and the submission of PROLIFT+M, and based on the unsuccessful commercial history of INTERGEL a PMA approved absorbable gel product, Ethicon should have had familiarity with the foreseeable risks for placement of absorbable materials in patients' bodies and difficulties with the body's re-absorption and elimination of the material and the inflammatory response which can be triggered and potential delay in healing. Ethicon's proposed new use for UltraPro mesh for PFR using the 510(k) process was going to

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[83] This superseded the Guidance for Resorbable Adhesion Barrier Devices For Use in Abdominal and/or Pelvic Surgery" of December 16, 1999. Issued by CDRH's "Obstetrics and Gynecology Devices Branch"(OGDB) and "Plastic and Reconstructive Surgery Devices Branch",(PRSB) ODE, CDRH,FDA. The Guidance describes the preparation for an IDE to pursue obtaining PMA approval. "Applications with primarily gynecologic indications(s) will be reviewed by OGDB."

[84] FDA's Guidance for Industry titled "Resorbable Adhesion Barrier Devices For Use in Abdominal and/or Pelvic Surgery"[84] issued June 18, 2002, (http://www.fda.gov/)

[85] FDA's Guidance for Industry titled "Resorbable Adhesion Barrier Devices For Use in Abdominal and/or Pelvic Surgery"[85] issued June 18, 2002,(http://www.fda.gov/)

significant expand the area of absorption and dose of poliglecaprone 25 beyond that of a suture or single sheet of mesh for abdominal hernia repair when used to repair the entire female pelvic floor. It was an issue that should have been known to Ethicon's material scientists which had already significantly underestimated safety and effectiveness of a PMA approved absorbable gel for indication in the female abdomen and pelvis for adhesion prevention that was not a product combined with a PE mesh.

196. As discussed above with the Truthful and Accurate Statement, all United States manufacturers submitting a 510(k) are required to sign the following statement to ensure that no material fact was not being provided to the FDA:

> *I certify that, in my capacity as the (position held in company) of (company name), I believe to the best of my knowledge, that all data and information submitted in the premarket notification are truthful and accurate and that no material fact has been omitted. ("As required by 21 C.F.R. § 807.87(k))*

197. However, the statements contained in both of Ethicon's 510(k)s (K071512, and K071512 S02) for PROLIFT and PROLIFT+M was modified. Ethicon's Section 6 of its September 19, 2007 submitted documentation, and original PROLIFT+M June 2007 submission signed by Bryan Lisa and Vincenza Zaddem did not include the same statement required of all other United States medical device manufacturers indicating that "no material fact has been omitted." The statement was modified despite no discussion in either the original 510(k) or the Amendment in September 2007 to alert the FDA's reviewer Ethicon had decided to change the certification statement to only apply to facts material to FDA's SE decision. FDA's Reviewer specifically requested that Ethicon's S02 be updated to address both Prolift and Prolift+M, which was not done. Without any explanation, or perhaps as an error in typing, Ethicon changed the statement in the original 510(k) submitted June 2007 and repeated the same error in wording and certification in its submission of September 19, 2007 significantly narrowing the truthful and accuracy scope only to the SE decision:

> *I certify that, in my capacity as Regulatory Affairs Project Manager for ETHICON, Inc., I believe, to the best of my knowledge, that all data and information submitted in this premarket notification are truthful and accurate and that no material fact related to a substantial equivalence decision has been omitted.*[86]

198. Despite Ethicon's not signing the required statement of 21 C.F.R. § 807.87(k) and FDA's lack of identification of the change, it is a criminal offense for Ethicon or any other medical device manufacturer to willfully make false statements to FDA pursuant to 18 U.S.C. §1001.

[86] ETH.MESH.00372370; *see also* ETH.MESH.0074859.

## XI. OPINION #6:

OPINION #6: ETHICON'S ACTIONS WITH PROLIFT+M CONTRIBUTED TO ITS MARKETING OF MISBRANDED PROLIFT+M PFR KIT WITH INADEQUATE TESTING, INSTRUCTIONS FOR USE AND WARNINGS.

**Applicable Regulations**: 21 U.S.C. § 352(a)(f)(1)(2); 21 U.S.C. § 321(n); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 801.109.

199. Despite changing the wording in Ethicon's Truthful and Accurate Statement (21 C.F.R. § 807.87(k)) in its PROLIFT/PROLIFT+M 510(k)), the slight change in wording of the statement and scope, did eventually get clearance of a 510(k) but did not insulate Ethicon from misbranding and marketing a misbranded commercial PROLIFT/PROLIFT+M device in the United States. The failure of Ethicon to accurately disclose and discuss with the FDA's reviewers the risks, benefits and history of PROLIFT procedure since 2005 does not shield Ethicon from selling a misbranding product. Misbranding of its marketed device to physicians included Ethicon's failure to provide material facts pursuant to 21 C.F.R. § 1.21 in its labeling and marketing used for PROLIFT/PROLIFT+M. Misbranding also constituted Ethicon's actions with its design and study for its 510(k) when its commercial products failed to perform or ensure it provided surgeons with adequate warnings and instruction for use 21 U.S.C. § 352(a)(f)(2). 21 U.S.C. § 321(n) is misbranding as a result of Ethicon's actions with its 510(k) interaction with FDA and then with commercial marketing (selling) PROLIFT and PROLIFT+M with labeling and advertising that was false and misleading in terms of Ethicon's statements, oral or written or implied for its commercial device. Ethicon's PROLIFT/PROLIFT+M was misbranded pursuant to 21 U.S.C. § 352(t) when Ethicon failed to adequately, accurately and truthfully provide the FDA with required material or information (reports), including material information in its 510(k) submission. Finally, even for a 510(k) cleared product, Ethicon, not the FDA, was required at all times to provide an adequate prescription label for its commercial product. 21 C.F.R. § 801.109. Ethicon did not perform the necessary studies, preclinical or clinical, for PROLIFT+M, it did not warn about the risks, including the volume of acceptable absorbable material implanted on the pelvic floor to be absorbed by the body, to ensure it was marketing a safe and effective and adequately labeled PROLIFT+M product after 2008.

200. Ethicon's 510(k) omitted relevant safety and performance information for FDA for PFR and then for physicians. Ethicon's 510(k) failed to advise the FDA about the known risks and benefits of its selected predicates, the clinical information available both for SUI and PFR mesh and relevant to FDA's consideration of Ethicon's PROLIFT/PROLIFT+M 510(k) for clearance without clinical data. Ethicon's September 2007 response to the FDA continued not to provide truthful and accurate disclosure of the risks and benefits of PROLIFT and PROLIFT +M. This failure to disclose did not give the FDA reviewer to consider the 510(k) application and request additional testing and data. Despite the material facts that PROLIFT Procedure had been available before 2006, that did not prevent Ethicon as a responsible manufacturer with a commitment to patient safety and quality from addressing safety issues as it addressed its design and testing of PROLIFT+M. As Ethicon knows, it remains a Prohibited Act (21 U.S.C. § 331(a)(b)) for Ethicon to sell a medical device in the

United States like PROLIFT+M that is not safe, effective and adequately labeled based on Ethicon's lack of adequate study and testing and post-marketing monitoring.

201. Dr. Robinson was asked in 2012 about the Patient Brochure and its lack of listing pain as a potential complication for a woman for PROLIFT and if Ethicon expected the patient to figure out independently their risk for continued (chronic) pain as a risk. His response was that the PROLIFT brochure was intended as a jumping off point for a discussion with the physician, it was not intended to be definite. *See* Robinson dep. 3/14/2012 at 457: 10-22. When asked if Ethicon thought patients rely on Ethicon to tell them the truth about the PROLIFT procedure in the patient brochure titled as applicable to PROLIFT, his response was, "As best we knew at the time we created it." Robinson dep. at 458:22-459:2.

## XII. OPINION # 7:

ETHICON DID NOT VOLUNTARILY UPDATE AND TIMELY CIRCULATE PROLIFT/PROLIFT+M LABELS TO PHYSICIANS WHICH FULLY NOTIFIED THEM OF CHANGES REQUESTED BY THE FDA.

**Applicable Regulations**: 21 C.F.R. § 807; 21 U.S.C. § 352(a)(f)(1)(2); 21 U.S.C. § 321(n); 21 U.S.C. § 331(a)(b); 21 C.F.R.§ 801.109; 21 C.F.R. § 820.

### A. ETHICON MODIFIED FDA'S REQUESTED CLINICAL PERFORMANCE SUMMARY TO INCORRECTLY IMPLY RANDOMIZED CONTROLLED STUDIES WERE BEING CONDUCTED FOR PROLIFT AND PROLIFT+M AND DOWNPLAY THE RISK INFORMATION GIVEN TO PHYSICIANS

202. FDA requested in its August 24, 2007 AI Letter to receive the clinical data available from the two (2) French studies. FDA was told in Ethicon's September 2007 (S02) response that there were 8 French study centers, as well as an additional 3 centers in the US. Ethicon indicated that it wanted to correct its original 510(k) that indicated only 2 French centers. Ethicon had submitted inaccurate information to FDA in the initial version of the Prolift+M 510(k), which was updated only after questioning by the FDA reviewer for clinical data.

203. In the September 2007 response, FDA received the requested clinical study for PROLIFT for eight (8) sites in France. The population enrolled 90 patients (85 with 12 month FU) and 12-months follow-up with GYNEMESH PS (reportedly not full final PROLIFT Kits) with 27 (30%) serious adverse events (SAE), of which 18 (20%) were considered related to the study device or procedure. There were 3 cases (4%) of post-op onset dyspareunia, and severe vaginal retraction was reported in 11 (13%) of patients, with visible or visible and palpable mesh exposure in 9 patients (10%), of which 5 underwent surgical intervention (5%). There were 16 failures at 12-months (19%) and 11 failures (13%) at 6-months, with 5 pts lost to follow-up.[87] French study "[t]he French study did not meet the criteria for success,

[87] ETH.MESH.00372483.

the study did demonstrate success rates comparable to the 30% of traditional vaginal prolapse repair."[88] French study: Protocol 2003-016 Clinical assessment of the TVM technique for treatment of genital prolapse. Final report of 12-month evaluation. "85" patients Final June 28, 2006. See discussion of Fatton and Jacquetin 2010(above).

204. In September 2007, FDA was also now informed by Ethicon of three additional (3) US centers conducting a "Post-marketing Study" for Ethicon. As post-marketing study not conducted under an FDA approved IDE, not provided and listed in NIH Clinical Trials Database, no signed financial disclosure statements, no adequate informed consent for the patient participants to ask permission to participate in Ethicon's research study with PROLIFT, no required monitoring or FDA approved protocol. However, despite the use of United States patients for conducting human research for Ethicon with an investigational device outside an approved IDE, there was no regulatory action by FDA's members of ODE.

205. These US sites were conducted by Ethicon called a "postmarketing study" which began in 2004. This post-marketing study was before the start of the French sites or the off-label launch of GYNEMESH PS for PROLIFT. The study cites the location and timeframe as: Topeka, KS, Milwaukee, WS, Allentown, PA. May 7, 2004 through December 12, 2005[89] . The subsequent publication was[90]Miller (2011) which had the following risk information for PROLIFT: RESULTS: 85 patients enrolled, but 66 with 5 year follow-up (78%) (19 patients lost to FU!). (Mesh exposure 16/66 (24%); dyspareunia 3/66 (5%). Success rate at 5 years 77%. Mesh exposure (erosion) was the most commonly reported complication along with 1 rectovaginal fistula and 2 ureteral injuries. The authors reported 5 patients requiring reoperation for POP at 5 years (8%).

206. FDA's December 20, 2007 AI Letter to Ethicon, after it reviewed the clinical data provided it (French +US) after it requested for PROLIFT (only) that Ethicon include a written Clinical Summary of the French Data from 8 centers. FDA determined that the French data was relevant to risk information for PROLIFT. Justification by FDA for inclusion of the clinical performance data in the label for physicians for PROLIFT was:

> *...seriousness of the reports in FDA's MDR database associated with Gynemesh A/P vaginal wall repairs.* [91]

207. FDA indicated that Ethicon could use FDA's write up (evaluation) of the French data as its template for preparing the US cohort data. "If the study can be pooled, you may wish to provide a single summary for both cohorts." (Assumption that it would be consistent with FDA's template). There was no reference by the FDA to future randomized controlled studies being conducted for PROLIFT:

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[88] ETH.MESH.00372350.
[89] ETH.MESH.00372564.
[90] Miller D, Lucerne V, Babin E, Jones P, Robinson. Prospective Clinical Assessment of TVM Technique by Treatment of POP, 5-year results. Female Pelvic Reconstr. Surg. May 2011 (17)(3):139-43.
[91] ETH.MESH.00372653; ETH.MESH.00372651.

FDA's template for Clinical Performance Data (a Summary of this data conveying the information available for PROLIFT was to be included in the PROLIFT Label)- the same could be used for US Data and if possible the pooled data:

*As of December 2007, no prospective, controlled clinical trials have been conducted to evaluate the safety and effectiveness of Gynecare Prolift as mechanical support or bridging material of the fascial defect in repair of vaginal wall prolapse. Limited data are available from a prospective, non-randomized, non-controlled observational study using Gynecare Gynemesh, a surgical mesh made of non-absorbable polypropylene as Gynecare Prolift. In the clinical study, the mesh was provided in pre-cut configurations however the insertion tools provided in the Gynecare Prolift kit were not available.*

**Study Results**

**Effectiveness:**

The study did not meet the pre-defined criteria for correction of prolapse of less than 20% (upper limits of 90% confidence interval). The observed rate of prolapse at 12-months was 18.4% (90% CI of 11.9-26.2)

PSI scores of vaginal prolapse improved from baseline (13.9 SD 5.7) to 12-months (1.9, SD 2.5). There was a trend to improvement of activities of daily living scores from baseline to 12-months post-operatively.

**Safety**

Moderate/severe vaginal retraction (12%)
Visible or visible and palpable mesh exposure (10%)
Surgical reintervention for mesh exposure (6%)
Urinary tract infection within 6 weeks post-op (17%)
Hematoma (5%)
Abscess (1%)
Vesico vaginal fistula (1%)[92]

208. Ethicon's February 22, 2008 (Supplement 04) response however, opted to use pooled PROLIFT US and the French data for its draft PROLIFT IFU. Ethicon's proposed CLINICAL PERFORMANCE had been significantly changed from FDA's original message about the limitations of the clinical data available (see above). Ethicon's proposed message was to inform physicians there were randomized controlled studies underway, studies applicable to PROLIFT started in 2004 and that there was some data available with successful treatment shown for polypropylene mesh used in Gynecare PROLIFT. Ethicon's message totally minimized and downplayed FDA's message about the limitations of data, unknown efficacy and risk:

*Randomized controlled clinical evaluations of the GYNECARE PROLIFT Systems are underway, but at this time preliminary data are available from two early observation studies of transvaginal mesh that were initiated in 2004. These observational studies*

[92] ETH.MESH.00372653.

> *evaluated a pre-cut surgical mesh made of the same non-absorbable polypropylene as the mesh used in the Gynecare PROLIFT System. For these studies, the mesh was provided in shape similar to that of the GYNECARE PROLIFT System, though implantation instruments were not provided in these studies. One of the two centers involved eight investigational centers in France; the second included three investigational centers in the US. ...*[93]

209. Ethicon's proposed draft CLINICAL PERFORMANCE label in February 2008 had no distinct heading of "Effectiveness or Safety" or a table to simplify the presentation of the information provided to the physician:

> *The 12-month postoperative study results were as follows (US, France): proportion of subjects with ICS Stage II or greater (12%, 18.4%), met pre-defined criteria of the upper limit of 90% CI less than 20% (yes,no), Prolapse Symptom Index (PSI) mean (6.6,3.1), Mean QOL score (0.7, 0.4)*
> *Adverse events, expressed as percentages, were as follows (US, France): hematoma (3.5,4.5), abscess (0, 1.1), urinary tract infection with 6 weeks post procedure (8.2, 16.9), mesh exposure (14.1,10.0), surgical intervention for mesh exposure (7.1,5.6), vesico-vaginal fistula (1.2, 1.1), recto vaginal fistula (1.0,0) and moderate/sever vaginal retraction (3.6, 12.6)*
> *More recent data specific to the GYNECARE PROLIFT System may be available in the published literature. Please contact your sales representative for more information.*[94]

210. Ethicon at no time in the 510(k) informed FDA that its business plan at the time of the PROLIFT/PROLIFT +M 510(k) intended PROLIFT sales to be cannibalized within 2 years by PROLIFT+M. Physicians were to favor using the 'light weight' PROLIFT+M over polypropylene mesh of PROLIFT. The Ethicon sales message (for example AUGS 2009 Sales deck was traditional polypropylene mesh) was to provide the benefits of PROLIFT+M over PROLIFT without having to perform any head-to-head comparisons of the two products. Any reference to the use of "polypropylene mesh" was to automatically imply to the physician inferiority of PROLIFT compared to PROLIFT+M (with Monocryl) delivery of less mesh. This message was despite Ethicon's lack of any study of benefits and risks for PROLIFT+M. This proposed statement for the PROLIFT label as requested by Ethicon in February 20, 2008 with the use of the "non-absorbable polypropylene" mesh as synonymous used in "PROLIFT" would assist Ethicon's future sales strategy to promote PROLIFT+M without requiring additional study.

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[93] ETH.MESH.00372672.
[94] February 22, 2008;ETH.MESH.00372668, ETH.MESH .00372673.

211. Under CLINICAL PERFORMANCE there also was no accurate discussion by Ethicon for FDA of the risk of mesh contraction identified since 2006 by the French PROLIFT Investigators with symptoms of dyspareunia, erosion, revision surgery or chronic pain. Ethicon's CLINICAL PERFORMANCE summary in the 510(k) did not include that by November 2006 PROLIFT's experts knew about the risk for mesh retraction with recurrence of POP and that anterior PFR risk was greater than posterior risk. Ethicon did not reference to FDA or the label that the French group was performing 2D ultrasound studies to quantifying mesh contraction in 2006 regarding patient risk for POP recurrence and vaginal changes.

212. Despite Ethicon's statement in the original June 2007 510(k) for PROLIFT+M, followed by FDA's statement in its August 24 and December 20, 2007 AI Letters of the lack of any clinical data for PROLIFT+M and that PROLIFT and PROLIFT+M clinical information should remain totally distinct, Ethicon proposed for its draft PROLIFT+M label of February 22, 2008 to directly adapt and use the PROLIFT CLINICAL PERFORMANCE statement for PROLIFT+M:

> *Randomized controlled clinical evaluations of the GYNECARE PROLIFT and GYNECARE PROLIFT+M Systems are underway, but at this time preliminary data are available from two early observation studies of transvaginal mesh that were initiated in 2004. These observational studies evaluated a pre-cut surgical mesh made of the same non-absorbable polypropylene as the mesh used in the Gynecare PROLIFT System.*[95]

## B. ETHICON DRAFTED AN ALTERNATIVE MORE MARKETING FRIENDLY STATEMENT FOR ITS LABEL THAN ORIGINALLY PROPOSED BY FDA TO CONVEY THE LACK OF SAFETY AND EFFICACY INFORMATION.

213. FDA in December 20, 2007 indicated that the draft IFU for PROLIFT and PROLIFT+M did not adequately address "usability and potential adverse events".[96] FDA proposed updating the label – IFU, contraindications, warnings, precautions, adverse reactions, performance, sterility, disposal and storage sections should be placed before the recommended surgical technique. FDA specifically requested that the label be updated to inform the physician on the lack of safety and efficacy information:

> *2.d. Please add, immediately about your indications statement, the statement*
> *"The safety and effectiveness of synthetic mesh or film support in transvaginal surgical procedures to treat pelvic organ prolapse have not been demonstrated in prospective, randomized clinical trials."*[97]

[95] ETH.MESH.00372683.
[96] ETH.MESH.00372651.
[97] ETH.MESH.00372650- ETH.MESH.00372651.

214. In January 22, 2008, Ethicon's response to the FDA's request for inclusion of FDA's "2.d", a statement which Ethicon could have agreed to immediately add as written by the FDA, Ethicon indicated inclusion would put it at a disadvantage with competitive device. FDA's Dr. Corrado that this IFU information (statement) would be enforced for the devices of this "nature in the future". FDA's Branch Chief Dr. Krause indicated that these changes were to be made to the device "across the board". Essentially FDA was telling Ethicon this should be considered a type of class statement required of all the TVM manufacturers. An internal FDA PMI (Post Market Issue) Action team had been formed at CDRH just to deal with the adverse events being associated with PFR meshes. This statement was a recommendation of FDA's PMI to address public safety. Dr. Krause indicated that Ethicon's PROLIFT+M submission was the first submission since FDA formed the PMI action team. [98]

215. Ethicon's February 22, 2008 response was to disagree with the use of the FDA's proposed statement in its draft label. Based on Ethicon's review of the available literature and several published studies, Ethicon did not think FDA's statement was accurate. Ethicon its use in the label would have the potential to impact payers for the product in the US and other countries. Ethicon reminded the FDA of its restriction to the least burdensome pathway for dealing with industry and continued:

> *Therefore, in order to take the least burdensome approach with the labeling, we proposed the following statement, which addresses how this device has been cleared to market in the US for both PROLIFT and PROLIFT+M.* [99]

216. For a 510(k) product, for which FDA does not write or approve the label, which is the responsibility of Ethicon pursuant to the Act, Ethicon proposed its alternative statement for the FDA's requested statement for Ethicon's label:

> *In the US, substantial evidence of GYNECARE PROLIFT Pelvic Floor Repair Systems to synthetic mesh with the same indication has been demonstrated through benchtop and pre-clinical testing.*[100]

217. FDA is held accountable for completion of its 510(k)s in a timely manner of 90 days. Therefore, a 510(k) that is not completed will be held against a Device Branch assigned the 510(k) as well as the annual reviews of each individual reviewer and the overseeing Branch Chief. Therefore, there is a sense of urgency to get a 510(k) completed by members of CDRH. CDRH's ability to adhere to required regulatory time frames is part of the annual review of CDRH by Congress calculation of MDUFA fees which industry will pay to CDRH.

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[98] ETH.MESH.00372662.
[99] ETH.MESH.00372666.
[100] ETH.MESH.00372666.

218. On May 4, 2008, FDA was trying to bring the Prolift/Prolift+M 510(k) which involved finalization of an agreement on the label. To help expedite the process, FDA proposed a compromise statement. It would agree to combining FDA's original requested statement with Ethicon's proposed acceptable statement. Ethicon on May 9, 2008 agreed to accept the latest FDA compromise statement for its product label, with no other changes made than the addition of a trade name rather than 'this mesh'. Once again the impact of the FDA's original proposed safety message for the product insert and the risk information for physicians about the limitations of the data was successfully minimized (not improved) by actions of Ethicon to market its product:

> *The safety and effectiveness of GYNECARE PROLIFT Pelvic Floor Repair Systems compared to conventional surgical repair for pelvic organ prolapse have not been demonstrated in randomized controlled clinical trials. In the United States, substantial equivalence of GYNECARE PROLIFT Pelvic Floor Repair Systems to synthetic mesh with the same indication has been demonstrated through benchtop and cadaveric testing.*[101]

## C. ETHICON DISAGREED WITH FDA REGARDING ITS NEED TO INCLUDE A PATIENT WARNING ABOUT LACK OF ADEQUATE INFORMATION ABOUT RISKS AND BENEFITS OF TVM POP

219. In its May 4, 2008 AI Letter, the final FDA AI letter before FDA's clearance of May 15, 2008, FDA proposed that Ethicon voluntarily add the following statement to its patient labeling to inform the patient directly of the lack of adequate clinical studies to known risk versus benefits of PFR for POP. This was similar to the message FDA had requested Ethicon voluntary include in the physician label which was significantly altered by Ethicon. This lack of data and adequate study and unknown risks and benefits of TVM for POP would be the same message sent directly to patients and physicians by its use of publicity, which was able to circumvent Ethicon's actions. FDA's Public Health Notification issued October 2008 to patients and physicians and the Public Advisory Meeting in September 2011 and the FDA' published notice for future reclassification of these devices to requirement for PMA approval in 2014 are all methods not dependent on Ethicon agreeing to voluntarily protect the public and ensure its own compliance with the Act. FDA requested that Ethicon voluntarily include the following statement in its patient labeling ( and brochure):

> *Synthetic mesh is a permanent medical device implant. There is not enough data from clinical studies to know whether the benefits of this implant is greater than the risks. Therefore, you should carefully discuss with your doctor and understand the pros and cons*

[101] ETH.MESH.00372737.

> *of mesh implants before deciding on a procedure to treat your condition.*[102]

220. Ethicon's May 9, 2008 response was that it disagreed with FDA's conclusion about there being a lack of data (preclinical and clinical). It disagreed with FDA that the data available was insufficient to determine whether the benefits of the device are greater than the risks. Ethicon proposed its alternative statement for use in its label telling the woman to discuss risks with her physician. However, FDA's point was that without data the physicians did not know the risks and benefits of the procedure to be able to provide to the woman for an elective procedure. Ethicon's alternative statement for its label:

> *Synthetic mesh is a permanent medical device implant. Therefore, you should carefully discuss with your doctor and understand the benefits and risks of mesh implant surgery before deciding how to treat your condition.*[103]

## D. ETHICON OBJECTED TO FDA'S REQUEST TO INCLUDE TWO SPECIFIC REFERENCE CITATIONS IN ITS LABEL

221. FDA's AI letter of December 20, 2007 made the following request of Ethicon:

> *Please add the following references to the last page of your labeling:*
> *Huebner M, Hsu, Y and Fennder DE. The use of graft materials in vaginal pelvic floor surgery. Inter Journ of Gynecol and Obstet 2006; 92:279-288*
> *Altman D and Falconer C. Peri-operative morbidity using transvaginal mesh in pelvic organ prolapse repair. Obstet and Gynecol 2007; 109(2, Part 1):303-308.*[104]

222. At a January 22, 2008, teleconference, regarding the two articles requested for the label by FDA, (one of which Ethicon originally referenced to FDA in its June 2007 510(k) for support of clearance), Ethicon indicated it did not feel the "need " to include references to the literature in its label, as the body of literature is continually updating. Dr. Corrado, FDA told Ethicon at the teleconference that she had selected these two specific articles since they both "…highlighted the issues associated with these devices."

223. In its February 22, 2008 response, Ethicon proposed instead of including the two references requested by the FDA, to have its label direct physicians to contact the sales representative for more recent information. Ethicon told FDA it thought it was inappropriate to point to these two articles in the label. Ethicon reportedly felt it was better to direct surgeons to obtain further information on TVM from the literature through Ethicon's sales representatives. This approach would reportedly let Ethicon maintain its currency of the

[102] ETH.MESH.00372737.
[103] ETH.MESH.00372737.
[104] ETH.MESH.00372651.

IFU as well as avoid the need to translate references to 28 languages. Once again, Ethicon proposed an alternative method which could downplay the impact of the FDA's request for the physician. Ethicon proposed the following statement for its label which would essentially inform a US physicians that clinical performance of mesh for PFR is in the published literature, something redundant and obvious to a US physician:

> *Additional information on the clinical performance of mesh for pelvic floor repair is available in published literature. Contact your company sales representative for assistance.*[105]

## E. ETHICON, DESPITE FDA'S REQUEST TO KEEP CLINICAL INFORMATION FOR PROLIFT OUT OF A PROLIFT+M LABEL, INCLUDED PROLIFT INFORMATION IN ITS PROLIFT+M LABEL

224. The FDA in its December 20, 2007 AI letter indicated that labeling changes for the PROLIFT+M label had not been made. FDA thought that since there were no clinical trials conducted for PROLIF+M but there was clinical data for PROLIFT, the device labeling should clearly distinguish between the two products and not combine the data. FDA wanted it to be stated that there was no clinical data existing for the new combination of absorbable/nonabsorbable material as used for PROLIFT+M.[106]

225. Ethicon's February 22, 2008 response appears to have disregarded FDA's concerns for physicians and proposed to include one statement in both PROLIFT and PROLIFT+M labels drawn for its proposed clinical summary of PROLIFT. This inaccurately implied that there was clinical data as a basis to support a new combination of products used in Prolift+M for PFR:

> *Randomized controlled clinical evaluations of the GYNECARE PROLIFT AND GYNECARE PROLIFT+M Systems are underway, but at this time preliminary data are available from two early observation studies of transvaginal mesh that were initiated in 2004. These observational studies evaluated a pre-cut surgical mesh made of the same non-absorbable polypropylene as the mesh used in the Gynecare PROLIFT System.*[107]

[105] ETH.MESH.00372667.
[106] ETH.MESH.00372737.
[107] ETH.MESH.00372668.

## XIII. OPINION #8:

ETHICON CONTINUED TO MARKET PROLIFT WITH AN INACCUARATE AND MISLEADING LABEL WHEN IT DID NOT IMPLEMENT AND CIRCULATE OR NOTIFY SURGEONS ABOUT CHANGES IN THE CLEARED FINAL LABEL UNTIL LATER IN 2009.

**Applicable Regulations**: 21 C.F.R. § 807; 21 U.S.C. § 352(a)(f)(1)(2); 21 U.S.C. § 321(n); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 801.109; 21 C.F.R. § 820.

226. On August 24, 2007, the FDA asked that Ethicon provide evidence to support its claim product claim that "bi-directional elastic property allows adaption to various stresses encountered in the body" in the IFU or delete it. Ethicon's response of September 19, 2007 was that it would agree to voluntarily delete the statement from its IFU.[108] In its follow up of the issue on December 20, 2007 FDA wrote to Ethicon that it was to confirm that the statement about "bi-directional elastic property allows for adaptation to various stresses encountered in the body" was deleted from its revised labeling.[109] On January 22, 2008, Ethicon teleconference meeting Minutes include: "B. Lisa also indicated that the PROLIFT IFU will be updated to remove the "bi-directional elasticity statement, unless justification can be provided in the response.[110]

227. Ethicon's February 2008 response to FDA's December 20, 2008 request to ensure the bi-directional statement had been removed from the label was to state that the requested statement had been removed from the IFU. Ethicon provided FDA with an updated IFU in Attachments I & II.[111]

228. However, despite Ethicon's assurances to FDA, the PROLIFT IFU would continue to retain the statement about bi-directional adaptation to various stresses in the body from December 17, 2007 through September 24, 2009, two years after Ethicon told FDA it would voluntarily remove the statement from the PROLIFT IFU based on a lack of its providing supporting data. Ethicon was required to market PROLIFT with the final label agreed to label with the FDA even for a 510(k) clearance.[112] It had been misleading (and misbranding) for Ethicon to assure FDA a statement would be removed (false claim) based on lack of supporting data and then provide FDA with an updated IFU having the statement deleted about claims for mesh properties, but continue to sell PROLIFT with the false and unsupported statement to physicians. This is an example of Ethicon's making a false benefit claim despite not having support or FDA clearance which is misbranding by Ethicon.

[108] ETH.MESH.00372351.
[109] ETH.MESH.00372651.
[110] ETH.MESH.00372662.
[111] ETH.MESH.00372668.
[112] ETH.MESH.02341454- ETH.MESH.02341455.

## XIV. OPINION #9:

ETHICON MARKETED PROLIFT SYSTEMS WITHOUT ADEQUATE STUDY, TESTING OR FOLLOW-UP TO LEARN THE CLINICAL '*CONSEQUENCES*' FOR PATIENTS OF MANUFACTURING CHANGES INTRODUCED FOR PROLIFT/ PROLIFT +M SYSTEMS.

**Applicable Regulations**: 21 C.F.R. § 807; 21 C.F.R. § 820.30; 21 C.F.R. § 820.70; 21 C.F.R. § 801.109; 21 C.F.R. § 812

### A. ETHICON'S 510(K) DID NOT FULLY ADDRESS FOR FDA THE CHANGES TO PROLIFT/PROLIFT+M MESH BASED ON IMPLEMENTATION OF LASER CUTTING

229. Laser cutting is a fast and cheaper way for a manufacturer to cut synthetic mesh than mechanical cutting. However, laser cutting produces changes to the edge of a cut polypropylene mesh which must be considered in the product design and intended use. FDA was told that both UltraPro and Gynecare PS had laser cutting. However, that was not an accurate statement, since it did not convey to the FDA reviewer that the history of use of laser cutting was "off label" for Ethicon's adoption of use of these two mesh products for PFR. Neither Gynecare PS nor UltraPro had been 510(k) cleared to be marketed with laser cutting as general synthetic mesh for hernia repair.

230. Like PROLENE, GYNEMESH PROLENE PS, UltraPro mesh had all been cleared by FDA for production by mechanically cutting flat mesh sheets. The sheets were intended to be trimmed by the implanting surgeon at surgery into the final desired size and shape for a hernia repair. Ethicon's TVT, PROLENE polypropylene SUI mesh kits are examples of mesh mechanically cut into narrow strips. These strips are implanted by the surgeon as slings for SUI. Beginning with PROLIFT, Ethicon's initial PRF product and then PROLIFT+M, the mash needed to be cut and assembled in more complex shapes for PFR. Ethicon changed its mesh manufacturing process to pre-cut pieces of mesh for PFR by laser cutting. It is a method which using a laser produces thermal (heat) effects along the cut edge as a result of melting of the plastic (polypropylene) by the laser. The melted mesh is thicker than the prior mesh for SUI and hernia repair.

231. The increased volumes of polypropylene laser-cut mesh for PFR was now intended to be implanted on a woman's pelvis floor, eventually stabilized by tissue ingrowth. However, the pelvic floor had the potential for motion and new forces in a living patient. The laser cut mesh had thickened edges. The pelvic floor introduced new pressures, including rubbing and grating of pelvic tissue. Thus PFR and use of laser cutting of PE mesh into new complex shapes introduced new and unaddressed issues of safety and effectiveness for PFR not seen with TVT (SUI) or the AMS predicates. These new issues were not studied by Ethicon. The change in manufacturing and proposed volume in terms of laser cutting of the edges was not adequately discussed with FDA in Ethicon's 510(k) in terms of changes in prior 510(k)s. Even more importantly than FDA, it was not addressed by Ethicon's material

scientists in clinical or pre-clinical studies in terms of the effects for an implanted female patient.[113]

### B. STERILIZATION BY ETHYLENE OXIDE (ETO)

232. For both PROLIFT and PROLIFT+M the final sterilization process of the surgical mesh for commercial release was changed from the prior cobalt irradiation of the predicate mesh 510(k)s(Gynecare PS and UltraPro) (as well as Ethicon's Prolene Mesh for TVT) to gas sterilization with Ethylene Oxide (ETO). ETO residuals unlike irradiation sterilization can trigger immune effects and reaction in patients from exposure to ETO as well as ethylene chlorohydrin.[114] Changing the volume of polypropylene mesh implanted in the female pelvis beginning with PROLIFT was another new safety issue when compared to TVT and SUI and the GYNEMESH PROLENE PS and ULTRAPRO predicates. The changes also required Ethicon to adequately control ETO levels of exposure and sterility implanted in patients in terms of quality controls for monitoring production bioburden and release sterility. For PMA approval of implanted products, ETO sterilization is one of the manufacturing controls usually described to FDA, including description of aeration conditions and time necessary for the product to reach specific levels, with the sponsor providing FDA with a dissipation curve as to acceptable residual levels of ETO and ethylene chlorohydrin.[115] Methods for controlling and measuring bioburden of production and support that adequate controls will be established will be described to ensure the final required sterility assurance level (SAL). Therefore, a change in sterilization methods for 510(k) is known to introduce new biomaterial issues and exposures for patients not seen with GYNEMESH PROLENE PS, ULTRAPRO or PROLENE for TVT (predicates), despite Ethicon's ability to bridge biocompatibility testing from other cleared 510(k)s. All medical device manufacturers selling sterile products under a 510(k) for implantation are still required to establish and adhere to its maximum set residual levels for fulfilling a required product Sterility Assurance Level (SAL) to permit commercial release, generally the SAL is $10^{-6.}$ . There must be periodic revalidation of sterility by a sponsor based on changes in production bioburden or changes in packaging or changes in the product necessitating revalidation of the sterilization cycle and SAL.

233. Using ETO sterilization for a 510(k) product did not relieve Ethicon from taking all the same quality assurance actions necessary for marketing a sterile PMA approved product.

### C. ETHICON CHOSE TO LABEL ITS PROLIFT IMPLANT AS 'NOT PYROGEN FREE'

234. Ethicon indicated that it intended <u>not</u> to label its PROLIFT/PROLIFT+M product as "pyrogen-free." Pyrogenicity testing defines the acceptable limit for detection of pyrogenic

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[113] ETH.MESH.00372640.

[114] ETO levels must conform to ANSI/AAMI/ISO 10993-7:1995 Biological Evaluation of Medical Devices-Part 7 Ethylene Oxide Sterilization Residuals (Sterility) (revised 8/20/1998) or comparable methodology and ANSI/AAMI/ISO document should be used with AAMI Technical Information Report (TIR) No. 19:1998.

[115] FDA, CDRH ORDB 510(k) Sterility Review Guidance 7/3/1997 (http://fda.gov/downloads/medicaldevices/deviceregualtionandguidance/guidancedocuments/ucm080212.htm)

substance (endotoxin produced by gram-negative bacteria), which can produce febrile reactions (fever) in implanted patients, immune reactions and adhesions. There is no gold standard as to the acceptable level of pyrogen for physicians. However, medical device manufacturers typically as part of good quality control procedures establish an acceptable upper limit and of pyrogens which trigger will manufacturing action levels. For pyrogenicity testing the medical device industry uses the USP Bacterial Endotoxin Test (Monograph 85) using Limulus Amebocyte Lysate (LAL) or Rabbit Pyrogen Assay (Monograph 151) to determine that levels of gram-negative bacteria available and acceptable when implanted in patients. Ethicon did not repeat the biocompatibility and pyrogenicity testing for finished PROLIFT/PROLIFT+M. Rather it opted to tell FDA it would identify the products as not intended to be labeled "pyrogen-free". Thereby, the 510(k) process permitted Ethicon not to commit its quality practices to ensure the PROLIFT/PROLIFT+M products released for patients were 'pyrogen free.'

### D. ETHICON HAD USED FDA'S RESORBABLE ADHESION BARRIER GUIDANCE FOR ABDOMINAL AND PELVIC SURGERY FOR MARKETING OTHER PRODUCTS INCLUDING THE REQUIREMENTS FOR TESTING BUT DID NOT APPLY THE SAME RECOMMENDATIONS TO PROLIFT+M'S DEVELOPMENT

235. As has been discussed (above) Ethicon was aware of the Guidance for Industry Guidance for Resorbable Adhesion Barrier Devices for Use In Abdominal and /or Pelvic Surgery in 1999 and 2002. Ethicon had approval to market a resorbable mesh by PMA (P880047) for Ethicon INTERCEED (TC7). INTERCEED was a knitted fabric made of cellulose (not polypropylene) which swells when it becomes wet and eventually forms a gel which is intended to be reabsorbed by the body from the surgical site within a period of days. INTERCEED is placed by a physician following abdominal or GYN/pelvic surgery to help reduce adhesions. The PMA was first submitted in 1988 and approved for Ethicon in September 1989 as an 'absorbable adhesion barrier', an adjuvant to abdominal and gynecologic pelvic surgery. Ethicon continues to sell INTERCEED with the last PMA supplement (S021) approved on July 21, 2015.

236. Ethicon's other absorbable product was for INTERGEL PMA. It was submitted in 1999 and Ethicon obtained PMA approval of GYNECARE INTERGEL Adhesion Prevention Solution (P990015) in November 2001, following a successful for Ethicon FDA CDRH Medical Devices Dispute Resolution Panel decision which recommended FDA's PMA approval. Subsequently GYNECARE voluntarily withdrew INTERGEL from the global market on April 16, 2003, claiming a user error. FDA's Safety Alert of the voluntary withdrawal for a product it had reservations about approving: "GYNECARE is withdrawing the device from the market to conduct a full and through assessment of technical issues, surgical techniques and circumstances associated with post-market events."[116]

[116] FDA April 16, 2003 Safety Alert- INTERGEL-Adhesion Prevention Solution- Urgent Global Withdrawal: GYNECARE INTERGEL Adhesion Prevention Solution Voluntarily Withdrawn for the market by GYNECARE Worldwide, http://www/fda/gov/medwatch/safety/2003/Intergel.pdf (last visited January 19, 2016).

237. Any medical device sponsor cleared by FDA to sell a product with overt marketing claims that resorption or absorption of its product, whether a film, gel, solution, reduced risks of adhesion or decreased a patient's response to a foreign body and/or surgery following abdomen or pelvis surgery, a product referred to as an "absorbable" barrier, carried a risk of FDA classifying the product Class III and requiring approval of a PMA or Product Development Protocol (PDP).[117] That product, unlike 'UltraPro mesh' or 'PROLIFT+M' as class II would require the sponsor conduct a clinical study with an FDA approved (IDE) (21 C.F.R. 812) and be approved by FDA. (21 C.F.R. § 814). Unlike the class II UltraPro and PROLIFT+M with implied claims of a possible health benefit from absorption, a PMA submission would require animal testing to support a reduced response, biocompatibility, physical and mechanical testing to support claims that product could lessen reactions in the body following abdominal or pelvic surgery.

238. The original 510(k) biocompatibility testing performed for Gynemesh PS and UltraPro meshes, now referenced by Ethicon for its Prolift/Prolift+M 510(k), did not have adequate testing to address the potential changes in performance and risk for the finished implanted mesh for PROLIFT and PROLIFT+M. The applicable testing should have been repeated for Prolift and Prolift+M to address the changes of ETO sterilization.

239. Studies for design validation and quality control for Prolift/Prolift+M 510(k) should have included in vivo studies to address new issues of tissue trauma associated with introduction of laser cutting, and immunologic response to ethylene oxide (ETO) for sterilization. Ethicon was required to develop and validate methods of quality control for ensuring acceptable bioburden and commercial release of adequately sterilized PROLIFT and PROLIFT+M. Physicians would not be able to adequately identify if the PROLIFT or PROLIFT+M mesh implanted had been adequately sterilized to a sterility assurance level (SAL $10^{-6}$) and the changes in mesh performance based on laser cutting.[118]

240. Ethicon's October 2007 information provided to the FDA regarding introduction of laser cutting and ETO's relaxation of mesh was all mechanical testing. As Ethicon should have known, the testing provided was not sufficient to determine the acceptability of these significant manufacturing changes 'in vivo' s as to the effects for a patient's tissue and product survival.

241. Ethicon's February 2008 response to FDA's request for additional testing for PROLIFT +M (December 20, 2007) indicated that GYNECARE PROLIFT+M mesh differs slightly from its base material ULTRAPRO mesh, with having laser cut as opposed to mechanically cut UltraPro, therefore, applicable mechanical testing has to be re-performed using laser cut PROLIFT+M as the base material (tensile strength, flexural rigidity, suture pull-out strength, Mullen burst strength, and tear strength). These demonstrate that PROLIFT+M has the properties substantially equivalent to UltraPro mesh. Ethicon however, performed no "in

[117] Ethicon's PMAs for GYNECARE INTERCEED (P880047) was approved July 2008 and GYNECARE INTERGEL (P990015) approved 2001 (voluntarily withdrawn from the global market April 16, 2003) INTERCEED is a cellulose sheet that once moist turns into an absorbable gel. Intergel was an absorbable solution. Both were FDA PMA approved as absorbable adhesion barriers for adjunctive use for Abdominal and GYN/Pelvic surgery.

[118] ETH.MESH.00372385 at 28.

vivo" testing which would address the tissue changes produced and risks for patients.[119] The same would apply to laser cutting of PROLIFT. Ethicon preformed inadequate testing and did not address the potential tissue changes for PFR.[120]

## XV. OPINION #10:

ETHICON'S MARKETING FAILED TO WARN PHYSICIANS THAT IT HAD NOT STUDIED THE SHORT- AND LONG-TERM RISKS, CHANGES IN TISSUE INGROWTH, PROPERTIES OF HEALING, INFLAMMATION, NAMELY "*CLINICAL CONSEQUENCES*" FOR WOMEN OF THE AMOUNTS OF ABSORBABLE POLIGLECAPRONE IMPLANTED BY PROLIFT+M MESH DURING PFR.

**Applicable Regulations**: 21 C.F.R. § 820.30; 21 U.S.C. § 352(a)(f)(1)(2); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 801.109; 21 C.F.R. § 820.20; 21 C.F.R. § 820.25. 21 C.F.R. § 812; 21 C.F.R. § 50

### *A.* ETHICON DISAGREED WITH FDA'S CONCERNS THAT ADDITIONAL TESTING WAS NEEDED BEFORE IT COULD CLEAR A PROLIFT+M 510(k). ETHICON HAD NOT STUDIED THE EFFECTS OF ABSORBABLE POLIGLECAPAONE WITH A POLYPROPYLENE MESH IMPLANTED IN THE PELVIC FLOOR. BASED ON CLEARANCE OF ULTRAPRO MESH AND THE LEAST BURDENSOME PROVISIONS ETHICON ARGUED THAT FDA COULD NOT MAKE IT PERFORM TESTING BEFORE CLEARING ITS PROLIFT+M 510(k).

242. In the August 24, 2007 FDA AI Letter Question #7 asked about the use of UltraPro mesh in the Prolift+M System mesh as a partially absorbable mesh, with ULTRAPRO intended for use in hernia repair. FDA saw these as significantly two different uses of ULTRAPRO in terms of anatomical location and the pathology treated between pelvic floor repair for POP and abdominal hernia wall defect reinforcement. FDA indicated that Ethicon's testing appeared in the PROLIFT+M 510(k) for June 2007 appeared inadequate:

> *The biocompatibility, bench performance, and animal testing that you have provided for the UltraPro Mesh is not sufficient to support the use of a partially absorbable mesh fir pelvic floor and vaginal wall prolapse repair. The tests do not support the successful use of the PROLIFT+M Systems for a complicated surgical procedure and placement of this device. Please provide a clinical evaluation of your proposed PROLIFT+M System to support your proposed Indications for Use.*[121]

[119] ETH.MESH.00372668-ETH.MESH.00372669.
[120] ETH.MESH.00372669.
[121] ETH.MESH.00372349.

243. Ethicon's response was to once again invoke the '*least burdensome provisions'* with FDA as support for the reason why additional testing was not necessary, it had not been requested of other manufacturers or for other 510(k)s and could not be required by FDA:

> *Historically the Least Burdensome approach to demonstrating substantial equivalence for hernia repair (PROLENE Soft Mesh K00122) to a mesh indicated for pelvic floor repair (GYNEMESH , K013718) has included comparative bench data on the mesh itself, biocompatibility assessment per ISO standards and animal/cadaver testing demonstrating no new issues of safety or efficacy are raised. This is consistent with the Surgical Mesh guidance provided by the FDA, "Guidance for the Preparation of a Premarket Notification Application for Surgical Mesh.*[122]

244. As not being correctly stated by Ethicon to the FDA in its 2007 response, the FDA's 1999 Guidance was written by FDA based on the traditional use of general surgical mesh in the abdomen for hernia wall repair. It represented FDA and industry's best thinking prior to 1999. The guidance listed elements which should be addressed and included in a 510(k) submission for FDA's consideration for clearance. The guidance was not intended to describe the testing and design needed by industry to develop a safe and effective mesh product. The entire 1999 Guidance had no discussion of surgical mesh intended for use for SUI or PFR procedure kits. There is absolutely no discussion of testing, design and use of surgical mesh for new transvaginal urogynecologic use as proposed by Ethicon for PROLIFT/PROLIFT+M. The FDA's Surgical Mesh Guidance was a nonenforceable guidance for Industry about "surgical mesh" not TVM mesh to help obtain 510(k) clearance. It was not meant by FDA to limit or restrict Ethicon's corporate testing necessary for it to develop a safe and effective TVM product.

245. The justification to FDA for not performing additional clinical trials is based on Ethicon's reportedly being unaware of potential new issues in safety and effectiveness. If that is indeed correct, then Ethicon's management has employed personnel at Ethicon that have inadequate training to make a correct determination about potential risk of products. *See* 21 C.F.R. § 820.20 and 21 C.F.R. § 820.25.

246. Ethicon had become aware of many new issues of safety and effectiveness with PROLIFT and PROLIFT+M which it knew were not addressed in the other surgical mesh products referenced by Ethicon. Therefore, with knowledge of "new issues of safety and effectiveness," the 510(k) process required Ethicon to conduct additional testing, whether

[122] Guidance for Industry and/or for FDA Reviewers/Staff and/or Compliance. Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh. March 2, 1999 The guidance provided "specific guidance regarding the information to be contained in a premarket notification submission for general surgical meshes…general surgical uses such as implantation to reinforce soft tissue where weakness exists (e.g. hernia repair, suture line/staple line reinforcement, muscle flap reinforcement, gastric banding, etc.) There is NO mention by FDA of a new intended use such as urogynecological mesh for PFR or SUI in this guidance. The guidance is not intended to provide design testing for a manufacturer wishing to market a urogynecological mesh.

preclinical, bench, or clinical trials to provide to the FDA for consideration of 510(k) clearance and to ensure safety and efficacy prior to patient use. By the 510(k) and the responses to the FDA, Ethicon had failed to adequately describe the risks for the products.

247. The August 24, 2007 FDA AI letter raised concerns about the absorbable material poliglecaparone contained in essentially a new combination mesh intended for PFR and that the absorption of the mesh for PFR reduced the implanted mesh strength by 33%. This was a new issue of safety and effectiveness not seen with any of the predicates. Also not addressed by Ethicon for the FDA in the 510(k) and material for the SE determination was that this new proposed use of UltraPro for 'PFR' raised a new issue of safety and effectiveness not seen with the two predicates Apogee or Perigee-{ which are both nonabsorbable mesh}. This new safety issue should have been addressed by a responsible medical device manufacturer, however, Ethicon did not perform additional pre-clinical testing, in vivo testing or clinical studies to quantify the amount (dose) of poliglecaprone acceptable for a PFR mesh in terms of the produced pelvic tissue response (first in animals and then in humans). Ethicon had a duty to determine if there would continue to be satisfactory tissue ingrowth to anchor the PROLIFT+M mesh in place in the pelvis for treatment of POP with poliglecaparone absorption (re-absorption).

248. Ethicon should have compared PROLIFT+M directly (head-to-head) to PROLIFT to characterize for FDA the performance of PROLIFT in a clinical trial to look for a positive or negative change in performance in patients. Both products should have been compared to traditional surgery, including Ethicon's ability to use a historical surgical outcome control, for matched sets of patients. Despite Ethicon's marketing goal to push next generation PROLIFT+M as better with LESS mesh than PROLIFT PFR System, the question becomes was there actually any support that the performance of PROLFIT+M was better or perhaps even worse or equal to PROLIFT.

249. Ethicon was required to have determined before commercial release to patients the acceptable volume of poliglecaparone for safe exposure for PFR in a tension free system based on acceptable tissue ingrowth and performance. Ethicon was responsible for ensuring the effectiveness of the TVM PROLIFT+M procedure to treat POP. As Ethicon's material scientists should have been aware its limited biocompatibility testing for clearance of an UltraPro mesh 510(k) for hernia repair, including a limited subcutaneous rat study (- which showed mesh contraction comparable to PE mesh PROLENE), did not provide sufficient information about Prolift+M. The limited testing with UltraPro mesh, despite being merely referenced in a 510(k) as the Least Burdensome method, did not address the real biomaterials issues for PROLIFT+M. Namely, Ethicon's UltraPro testing was not designed to address the effectiveness for PFR for a patient in terms of tissue ingrowth, poliglecaprone resorption, and inflammatory response. It should have been obvious to Ethicon's Material Scientists that new testing was required for PROLIFT+M for PFR. Ethicon provided FDA with Response #7, still incorrectly maintaining that additional clinical studies were not necessary for clearance of its 510(k), further incorrectly downplaying the clinical differences in risks and performance by telling the FDA's nonclinical reviewer that hernia and pelvis floor both had similar fascial tissue, totally ignoring to describe the differences in environment, tendency for motion, stresses placed on the implants, volume of resorbable

material delivered and needed to be cleared, the design of the implanted mesh and differences in blood flow:

> *…Although the anatomical location from hernia repair to pelvic floor repairs differs, the fascial tissue in the abdomen is comparable to that in the pelvis…*[123]

250. Ethicon may have been able to obtain 510(k) clearance for PROLIFT+M without performing additional testing but that does not ensure it will market a safe and effective product when implanted in women. The same information still needed to be determined regarding the acceptability of the design and effects of poliglecaprone for PFR as to ensuring the success of the commercial product for a patient. Products fail commercially when used in patients despite having a 510(k) clearance, just as Ethicon's Intergel product failed commercially in 2003 when used in living patients despite Johnson & Johnson's being able to compel a PMA approval from FDA. The scope of a product's life and adequacy of design and production lies far beyond an initial FDA clearance or approval to enter the market.

## B. ETHICON'S LABEL IMPLIED THAT ULTRAPRO'S MESH HERNIA TESTING RESULTS IN ANIMALS WERE IN SOME WAY APPLICABLE TO PROLIFT+M TVM POP IN WOMEN

251. Ethicon's 510(k) and interactions with FDA did not convey the 2006 findings of Ethicon's Experts in PROLIFT in terms of the risks associated with mesh contraction. In 2006 the French experts were using 2D ultrasound (as published in English in 2010) to look specifically for PROLIFT mesh contraction and to attempt to correlate performance and risks with detectable mesh contraction on imaging. The contraction effects were identified by 2D ultrasound to be worse for anterior PFR, with a greater risk for recurrent POP than posterior. Ethicon had also determined that the use of ULTRAPRO Mesh for PROLIFT+M would not address the mesh contraction and risk issue.

252. Ethicon eventually provided an ULTRAPRO 510(k) subcutaneous rat study to the FDA in Ethicon's submission of September 2007 (S02). However, the significance of the rat study findings regarding the already known risk of mesh contraction was not adequately described to FDA's reviewers, including the potential impact of contraction findings on PROLIFT+M performance. Ethicon knew since 2006 that ULTRAPRO would contract and that the contraction in PFR would contribute to erosion, dyspareunia, and pain. Ethicon's subsequent February 2008 PROLIFT+M draft label did not inform physicians about the animal studies (in vivo) studies were with ULTRAPRO a product intended as hernia mesh not for TVM and that the results were not transferable. As not discussed adequately in the 510(k) or with FDA, instead of risk information about potential for contraction, under PERFORMANCE the physician is told based on wording appropriate for an UltraPro hernia mesh IFU, there will be acceptable tissue ingrowth and mild inflammatory response For

[123] ETH.MESH.00372349.

PROLIFT+M with PFR. No such studies had been done for PROLIFT+M for PFR and there was no support that the hernia studies were applicable to PFR:

> *Animal studies show that implantation of GYNECARE GYNEMESH M Mesh elicits a minimum to mild inflammatory reaction which is followed by collagen tissue ingrowth through the mesh, thus incorporating the mesh into adjacent tissue. The mesh remains soft and pliable, and normal wound healing is not noticeable impaired.*[124]

253. Ethicon directly referenced its ULTRAPRO rat subcutaneous skin study (included in its September 2007 response to FDA). Without any data for the volume of mesh and Monocryl for PFR and in vivo data about the absorption of Monocryl burden in the pelvis, Ethicon chose to tell physicians that PROLIFT+M for 'PFR' behaved just like absorbed material in ULTRAPRO strips implanted in the back skin of a rat or Monocryl suture. Based on a rat study and Monocryl, the poliglecaparone would be totally absorbed from a woman's pelvis by 84 days. In terms of PROLIFT+M future marketing, there should be less mesh remaining in a woman following PFR by 84 days. (i.e." LESS mesh"). However, physicians were not informed in this section of the label or warnings or precautions that Ethicon had performed no study to actually determine the rate and effectiveness of poliglecaparone absorption in the pelvis for PFR. Ethicon developed no data to determine the biological effects or outcome of a PFR poliglecaparone burden in a woman's pelvis post PFR.

254. Ethicon's rat study for the ULTRAPRO 510(k) was insufficient support to design, develop and test the adequacy of the design of PROLIFT+M for commercial use. The Ethicon PERFORMANCE second paragraph reflected the use of ULTRAPRO as a trimmable surgical hernia mesh sheet not as Ethicon proposed use of PROLIFT+M as pre-cut mesh:

> *The polypropylene is not absorbed, nor is it subject to degradation or weakening by the action of tissue enzymes. In an animal model, excessive connective tissue deposition and deleterious scar plate formation did not occur. The mesh construction permits trimming of the implant without unraveling.*[125]

## XVI. OPINION # 11:

ETHICON DID NOT DISCLOSE TO FDA THAT ETHICON'S 'LIGHTNING PROJECT' WAS MARKETING'S PLANS TO MAKE UNSUPPORTED CLAIMS OF 'SUPERIORITY' FOR PROLIFT+M AS A 'LIGHTER' MESH TO DRIVE OBSOLESENCE OF PROLIFT FOR POP IN TWO YEARS.

[124] ETH.MESH.00372358.
[125] ETH.MESH.00372690.

**Applicable Regulations**: 21 C.F.R. § 807; 21 C.F.R. § 801.109; 21 C.F.R. § 1.21

255. It would have been significant to FDA as it reviewed the combined 510(k) for PROLIFT and PROLIFT+M that Ethicon intended to have PROLIFT+M be marketed with claims that it was somehow "superior" or an improvement to PROLIFT. FDA's review of both products was that both were to be viable equivalent Ethicon products when sold by Ethicon. There was actually more clinical data for PROLIFT than for PROLIFT+M. There was no information provided to FDA to indicate that it should review PROLIFT+M as superior to PROLIFT and it would be favored by Ethicon's sales force marketing over PROLIFT with implied new benefits. As a former Chief Medical Officer in ODE and current regulatory consultant, I would have found such information about future marketing plans to be significant as I reviewed labels proposed by Ethicon for PROLIFT and PROLIFT+M. It would also have been significant since FDA was still able to request a head to head comparison of the two products to ensure that PROLIFT+M actually provided a meaningful clinical benefit when compared to PROLIFT for PFR in terms of Ethicon's future marketing.

256. In terms of the commercial marketing of PROLIFT +M, as Scott Hamilton Jones testified in 2012, Ethicon anticipated that PROLIFT+M would cannibalize (replace) the PROLIFT PFR market within two years after FDA's clearance of a new PROLIFT+M 510(k) in 2008.[126] When asked if that would happen in the real world if physicians thought PROLIFT +M was better than PROLIFT, he answered "I imagined that's true."[127]

257. Dr. Robinson testified that PROLIFT+M was developed as a "design improvement" of the PROLIFT and in particular, to "minimize the mesh load given to the patient and increase the flexibility of the mesh being used in the pelvis with the expectation this would benefit the patient."[128] Despite there never having been a head-to head (HTH) comparison of PROLIFT versus PROLIFT+M by Ethicon or a full discussion with FDA of Ethicon's plan that Ethicon's sales force market PROLIFT+M to physicians implying it was replacing an older polypropylene mesh commercial product. Ethicon's Sales force was not to specifically indicate PROLIFT directly in discussion with surgeons but to reference favorable comparison of PROLIFT+M to traditional polypropylene (PE) mesh. The implication with the sue of PE mesh was that it was a reference to "PROLIFT". Based on early 3-month data, Ethicon at the AUGs 2009 meeting in its "AUGS Briefing Deck" intended for Ethicon's sales force to present PROLIFT+M – 'coated with Monocryl'—showed improved results for de novo dyspareunia and sexual function based on three-month interim data. This was to imply that PROLIFT+M with Monocryl had been scientifically shown to have better outcome than other products without Monocryl. However, there was absolutely no data to support claims of short or long-term effects associated with the presence of Monocryl. There were no marketing claims for the benefits of Monocryl included in Ethicon's 510(k) for clearance by the FDA. Therefore, any marketing claims which implied added benefits of

[126] Scott Hamilton Jones 1/25/2012 at 733:3.
[127] Scott Hamilton Jones Dep. 1/25/2012 at 733:10.
[128] Robinson Dep. 3/14/12p 15:7-20, 24-16:13.

Monocryl for PFR were supported by substantial evidence and are false and misleading, examples of misbranding.

258. The key marketing message for Ethicon's sales force in 2009, without having actually obtained any supporting clinical data was that there would be better performance of "PROLIFT+M" when indirectly compared to traditional polypropylene mesh. PROLIFT+M was presented as Ethicon said to FDA in the September 2007 response that PROLIFT+M, as having "better handling properties than polypropylene" and "better tissue integration-more flexibility when compared to polypropylene mesh." However, to the FDA in a discussion of a new and un-implanted mesh, the Monocryl coating provided only at the time of implant mechanical stiffness for a thin synthetic surgical mesh. There was no evidence provided to FDA that the presence of the Monocryl provided any lasting benefit for a patient with implanted mesh. In fact, the FDA, the Monocryl when implanted in the patient, raised additional unanswered risks which Ethicon had failed to address. Incorrectly, physicians were told that because the pores of PROLIFT+M were more open than polypropylene mesh (once the Monocryl has been completely gone-re-absorbed), without filaments that intersect or cross in the middle, more tissue could theoretically be incorporated (secondary tissue ingrowth). An attribute for marketing PROLIFT+M was "**LESS"-** 46% less mesh at 84 days, 55% less inflammation in surrounding tissue compared with pure polypropylene 28 days after implantation, 75% of sexually active patients with pre-procedure dyspareunia reported resolution in a 3-month interim data. PROLIFT+M was also stated to "resist wrinkling and folding during placement", again without any evidence and not supported by PROLIFT.

259. The AUGS Briefing Deck message for Ethicon's sales force: "PROLIFT+M with MONOCRYL* Suture material: Designed with more flexibility to help deliver improved functionality with less foreign material left in the body. That way, you and your patients can get more with less." The study that was used compared PROLIFT+M to traditional polypropylene mesh.

## XVII. OPINION #12:

ETHICON WAS OFFICIALLY TOLD BY FDA'S ODE IT MARKETED MISBRANDED AND ADULTERATED PROLIFT KITS WHEN IT BEGAN SALES IN THE UNITED STATES WITHOUT 510(K) CLEARANCE FOR TVM POP. ETHICON WAS TOLD BY FDA THAT CONTINUED MARKETING OF PROLIFT FOR TVM POP BEFORE 510(K) CLEARANCE OR OUTSIDE AN FDA APPROVED IDE (AUGUST 24, 2007 THROUGH MAY 15, 2008) DID NOT COMPLY WITH THE ACT. YET, AT NO TIME UP THROUGH MAY 15, 2008 DID ETHICON EVER INFORM SURGEONS AND WOMEN THAT ETHICON PROMOTED PROLIFT FOR TVM POP, AN INVESTIGATIONAL PRODUCT, OFF LABEL AND WITHOUT FDA'S PRE-MARKETING CLEARANCE.

**Applicable Regulations**: 21 U.S.C. § 352(a)(f)(1)(2)(t); 21 U.S.C. § 321(n); 21 U.S.C. § 331(a)(b); 21 U.S.C. § 351; 21 C.F.R. § 807; 21 U.S.C. § 360e

260. Once Ethicon was officially informed by FDA a 510(k) was required for PROLIFT, Ethicon was on official notice that despite its unapproved sales, PROLIFT was a class III investigational device and could only be available in the United States under an FDA approved IDE with the patient receiving adequate informed consent that the product had not been identified as safe and effective. Ethicon was on written notice from FDA that it could no longer legally sell Prolift until it obtained 510(k) clearance. Technically, the product had been a Class III investigational product since launch in 2004, but with FDA's official decision, there was absolutely no doubt that it could not be legally sold in the United States.

261. Any action by Ethicon that continued marketing of PROLIFT over the period August 24, 2007 through May 15, 2008 did not comply with the FD&C Act and implementing regulations and was the marketing of an adulterated device. (21 U.S.C. § 351). With this knowledge, Ethicon did not communicate to hospitals, distributors or physicians that without a 510(k) clearance, PROLIFT PFR Kit should be withdrawn from the market and not implanted in patients. PROLIFT had been implanted in patients without FDA clearance and as such were investigational devices for which the safety and efficacy was not known. The public communication to physicians would have informed them that PROLIFT, despite Ethicon's representations since 2004 to them was not a device cleared by FDA for PFR. This extremely important information would have assisted the physician to determine to use another cleared device or alternative procedure for elective treatment of POP, or to wait (delay surgery) until either Prolift or Prolift+M were legally cleared to be implanted in their patients. It would have also alerted physicians (and competitors) that Ethicon had promoted the use of TVM PFR products for POP that had not obtained clearance or approval from the FDA.

## XVIII. OPINION #13:

ETHICON'S DECISION TO STOP ALL SALES OF PROLIFT/PROLIFT+M (DE-COMMERCIALIZE) ALSO STOPPED ALL ETHICON'S EFFORTS TO COMPLY WITH FDA'S 522 ORDER. ETHICON'S MANAGEMENT CHOSE TO DISCONTINUE SALES OF PROLIFT+M RATHER THAN OBTAIN SCIENTIFIC POST-MARKET SAFETY AND PERFORMANCE INFORMATION ABOUT THE PRODUCT FOR FDA, PHYSICIANS AND PATIENTS.

**Applicable Regulations**: 21 C.F.R. § 820.198; 21 C.F.R. § 820.250; 21 C.F.R. § 803; 21 C.F.R. § 820.100; U.S.C. § 352(a)(f)(1)(2); 21 U.S.C. § 321(n); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 801.109; 21 C.F.R. § 822.3(j); 21 U.S.C. § 360l

## A. FDA ISSUED A 522 ORDER IN JANUARY 2012 TO ETHICON REQUIRING IT OBTAIN POSTMARKET PERFORMANCE INFORMATION TO UPDATE THE RISK INFORMATION AND LABEL FOR PHYSICIAN AND PATIENT LABELING FOR PROLIFT+M.

262. FDA wrote to Ethicon that it was concerned with potential safety risks for Gynecare PROLIFT+M Pelvic Floor Repair Systems (K071512) as evidenced by the adverse events reported to the FDA and in the published literature. In addition, the FDA was concerned with published literature indicating lack of added clinical benefit compared to non-mesh repair. Section 522 of the FD&C A, 21 U.S.C. § 360l authorized FDA to require a manufacturer to conduct postmarket surveillance of a class II or class III device. PROLIFT+M as a class II device met two of the requirements for a 522 Order from FDA:

> *Its failure would be reasonably likely to cause mesh erosion (i.e. organ perforation), severe pain, and fistula formation, which would meet the definition of "serious adverse health consequences" at 21 C.F.R. § 822.3(j). In addition, your device is intended to be implanted in the body for more than one year.*[129]

263. FDA recommended the use of a randomized clinical trial ("RCT") or prospective cohort study design to obtain data. The design compares a device (s) (Prolift+M) to a control (e.g. transvaginal urogynecologic surgery without use of mesh) through 3 years of follow-up. In lieu of one of the study designs recommended above, FDA also permitted Ethicon to develop a new sponsor registry or RCT/cohort study nested within a registry to address the public health questions, either as a single institution or in collaboration with other sponsors. FDA indicated it was amendable to Ethicon's facilitating creation of a multi-sponsor registry to address these public health questions. Therefore, the FDA expressed its openness and willingness to discuss alternative methods with Ethicon to obtain the post-market safety and efficacy information FDA wanted for the performance of these devices.

264. According to FDA, the clinical experience gathered from postmarket surveillance study may lead FDA to, among other things, recommend label changes regarding the use of a device. FDA indicated it was still considering the FDA's Advisory Committee panel's recommendations in 2011 that urogynecologic surgical mesh used for transvaginal repair of POP be reclassified from class II to class III. A reclassification would require clinical data to be obtained for approval of a PMA. Beginning in 2011, the FDA first requested Johnson & Johnson and Ethicon voluntarily conduct TVM post-market studies. The FDA then required the studies be conducted in its 2012 522 Orders sent to Ethicon. However, as will be discussed, Ethicon selected an alternative path to not conduct the 522 post-market

[129] ETH.MESH.03730582; *see also* Final Document: Global Harmonization Task Force, Post-Market Clinical Follow-up Studies, February 18, 2010 (GHTF/SG5/N4:2010), Section 5 (listing the following circumstances as examples for when a manufacturer needs to conduct postmarket surveillance: significant changes to device design or labeling, higher risk anatomical location, severity of disease/treatment challenges, questions of ability to generalize clinical investigation results, unanswered questions of long-term safety and performance, risks identified from the literature or other data sources for similar marketed devices, sensitivity of target population, training/learning curve issues, and emergence of new information relating to safety or performance).

studies, while at the same time continuing to market the products without post-market safety data, permitting women to continue to be implanted with its products.[130]

265. FDA, to entice Ethicon to complete a robust post-market study for Prolift+M, and based on FDA's plans to call for a future PMA for continued marketing, suggested Ethicon may want to consider the data requirements that would be necessary for obtaining clearance of a future PMA for PROLIFT+M in the design of its 522 study for PROLIFT+M. The same data, with appropriate planning by Ethicon could be used (as part of the Least Burdensome provisions) to support a PMA as well as complete a 522 study. If approval of a future PMA was a possibility for Ethicon for its PROLIFT+M that should be indicated in the cover letter to FDA accompanying Ethicon's submitted 522 study plan to better facilitate FDA's review.

266. FDA concluded its 522 letter that failure of a manufacturer to meet its 522 obligation was a Prohibited Act which misbranded its device and could result in regulatory actions by FDA:

> *Failure of a manufacturer to meet its obligations under section 522 is a prohibited act under section 21 U.S.C. 331(q)(1)( C). Further under 21 U.S.C. 352(t)(3) a device is misbranded if there is a failure or refusal to comply with any requirements under section 522 of the Act. Please note that violations of section 331(q)(1)(C) or 21 U.S.C. 352(t)(3) may lead to regulatory actions including seizure of the product, injunction, prosecution, or civil money penalties.*[131]

267. On April 2, 2012, Ethicon received a letter from FDA rejecting its proposed study design for the 522 study.[132] The reason for the rejection was the lack of sufficient information provided to FDA to allow it to complete its review. There were ten items still to be address in the letter by Ethicon about the PROLIFT+M proposed postmarket study.

268. On May 7, 2012, Ethicon sent a letter to the FDA advising it about Ethicon's decision to 'decommercialize' (stop sales) of PROLIFT+M and PROLIFT products. Ethicon requested that the Office of Surveillance and Biometrics (OSB), an Office in Compliance, place Ethicon's 522 orders **on 'hold'**. Placement on regulatory 'hold' by the FDA is a request to stop the regulatory clock. The time of an application being placed on 'hold' is effectively no longer held against CDRH or the involved members of CDRH, including OSB. At this time OSB was having to deal with all the 522 orders it issued in 2012 for TVM products for PFR.

269. FDA was to communicate back its confirmation to Ethicon of this plan to place the issue officially on regulatory hold. An internal May 13, 2012 email from Tim Schmid to Chuck Austin. "Subject RE: Final Communication Package." The discussion in the email was about the confidential information to be distributed about Ethicon's decision to decommercialize PROLIFT, PROLIFT+M, PROSIMA and TVT-Secur:

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[130] Dep. of Ron Horton, 7/1/2015, 345:22-346:7; *Id.* at 346:9-20.
[131] ETH.MESH.03730582.
[132] ETH.MESH.04567040.

> *They [Gynecare employees] will not be surprised by this decision but this will understandably fuel concerns regarding the attractiveness of the business and their role in the new world.*[133]

270. Ethicon's US Commercialization Decision was a US Discussion Guide for Use with Customers (Implanting Surgeons) on May 15, 2010. The document was intended to provide support for how to handle fact-to-face meetings with ALL pelvic floor repair and incontinence surgeons (customers). Document identifies the reason for discontinuation of the product as a "business decision." There is no information provided to physicians or women that the stopping of sales was due to a safety issue. Also without obtaining 522 post-market safety data, there will be no development or publication by Ethicon of the depth of the safety and performance of the removed products.

> *I also want to stress that this is not a recall, and not based on product safety. We stand behind the safety of our products. It is not necessary, based on this notification, for you to notify patients who have received these products, or for patients who have received these products to take any action.*[134]

271. In addition, after the decision to decommercialize this product, Ethicon and Johnson & Johnson formulated an extensive plan, under the leadership of Ron Horton, about what to tell the doctors who were using the product, a do's and don'ts guide.[135] Admittedly, Ethicon also informed the doctors "not to tell women who they'd already implanted with the [product] that the company had decided to discontinue selling the product."[136] They ultimately decided to take this approach because it decided that its product was safe and effective[137] even though the FDA experts determined that the products' safety and efficacy had not been established.[138] By not completing a 522 study or pursuing a PMA, there would be no Ethicon post-market generated data (evidence) to refute Ethicon's claims that its decommercialized products, including Prolift and Prolift+M were all safe and effective, but sales were only stopped only as a business decision.

272. The new indication for use of Ethicon's Gynemesh PROLENE PS as of September 28, 2012 was for "transabdominal" placement of Gynemesh PROLENE PS for apical vaginal repair for POP. Since the Gynemesh PROLENE PS mesh was no longer indicated for PFR as transvaginal placement for POP (as used in PROLIFT), there would be no requirement for Ethicon to conduct a 522 post market surveillance study for Gynemesh PROLENE PS.

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[133] ETH.MESH.04984186- ETH.MESH.04984188.
[134] ETH.MESH.05598522.
[135] Dep of Ron Horton, 7/1/2015 at 420:16-421:3.
[136] Dep. of Ron Horton 7/1/2015 at 429:14-25.
[137] Dep. of Ron Horton 7/1/2015 at 430:2-4.
[138] Dep. of Ron Horton 7/1/2015at 430:5-7; *Id.* at 420:14.

## XIX. CONCLUSION

273. Based on my professional experience, knowledge, and training and my review, evaluation, integration, and synthesis of the information identified and discussed in this Report, including the materials and scientific/medical literature specified, it is my professional opinion, made to a reasonable degree of scientific and professional probability, that Ethicon and Johnson & Johnson did not comply with those duties required of a reasonably prudent medical device manufacturer with its development and marketing of TVM Prolift+M System for POP in the United States.

274. Ethicon failed to evaluate the foreseeable risks and confirm the safety and effectiveness of the Prolift +M System in clinical trials prior to marketing these devices in the United States, despite the foreseeable risks for TVM POP seen with its Prolift System. Ethicon chose not to consider the experience and risks associated with its years of off-label promotion and use of Prolift for POP and did not conduct clinical trials prior to implementing full market release of Prolift+M in the United States in order to ensure safety and efficacy and update physicians and women on the risks. The labeling for Prolift +M System was inadequate and misleading and failed to warn physicians of the difficulties with the blind insertion for PFR, the difficulties experienced with use of the Prolift+M insertion tools and the significant learning curve seen in physicians already familiar with this type of surgery. The Prolift+M labeling was inadequate in multiple ways, including inadequate directions for use, inadequate warnings and lack of adequate information about potentially serious, permanent and life-altering risks for the product when implanted for TVM PFR. Additionally, Ethicon did not adhere to its own non-delegable responsibilities for implementation of adequate monitoring, complaint analysis, adverse event reporting, taking appropriate corrective and preventive actions to minimize risk and communication with physicians.

275. Ethicon marketed its Prolift System in the United States for TVM PFR prior to obtaining any 510(k) clearance. It did not adhere to current safety and ethical standards and, notably, the company's code of conduct to conduct business with integrity and do the right thing, including following the applicable industry standards. Both the physicians to whom the devices were provided and the patients in whom these devices were permanently implanted lacked the necessary information to make an informed decision about accepting the risks versus the benefits of using these devices instead of alternative methods for elective TVM treatment of POP.